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PATENT 1304-1-

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT : Henry E. Young and Paul A. Lucas
SERIAL NO.: 09/668,508 EXAMINER : Thaian N. Ton
FILED : September 22, 2000 ART UNIT : 1632
FOR : PLURIPOTENT EMBRYONIC-LIKE STEM CELLS, COMPOSITIONS,
METHODS AND USES THEREOF

CERTIFICATE OF MAILING UNDER 37 CFR 1.8

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450 on July 11, 2006.

Christine E. Dietzel, Reg. No. 37,309
(Name of Registered Representative)


(Signature and Date)

DECLARATION UNDER 37 CFR 1.132

COMMISSIONER FOR PATENTS
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Sir:

I, Henry E. Young, Ph.D., hereby declare and state that:

1. I am an inventor of the invention disclosed and claimed in the above-identified Patent Application.

2. I am presently employed by Mercer University School of Medicine, where I have been employed since 1988, most recently as a Professor of Anatomy in the Division of Basic Medical Sciences.

3. Education:

- (a) B.S.: Ohio State University
- (b) M.S.: University of Arkansas
- (c) Ph.D.: Texas Tech University
- (d) Postdoctoral: Case Western Reserve University

4. I have advanced training in Cell Biology, Developmental Biology, Zoology, Anatomy, and Biochemistry. I am also the author of more than 40 peer reviewed articles and six book chapters (*also see my Curriculum vitae submitted herewith and attached as Exhibit A*).

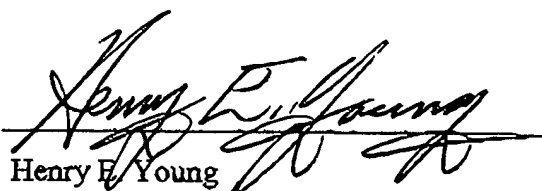
5. I have participated in and co-supervised the research that culminated in the data described and published in the article entitled "Adult-Derived Stem Cells", published June 2005 (Young, H.E. and Black, A.C. *Minerva Biotech* (2005b) 17:55-63), attached hereto as Exhibit B.

6. The attached paper "Adult-Derived Stem Cells" describes the various categories of stem cells located within adult or postnatal tissues, particularly including: differentiated cells (DCs), progenitor cells (PCs), germ layer lineage stem cells (GLSCs), epiblast-like stem cells (ELSCs) and recently identified blastomere-like stem cells (BLSCs). This paper states and confirms that ELSCs or epiblast-like stem cells, adult-derived pluripotent stem cells as designated and isolated by myself, can form somatic cell types from all 3 primary germ layer lineages, but will not form the sperm or ova. This is described in the paper, for instance, in the Abstract and in Table I, where it is noted with regard to cell types formed by ELSCs: "All somatic cells only, will NOT form gametes". In contrast, the described BLSCs form all somatic cells and spermatogonia, as noted in the text and in Table I (Young and Black, 2005b). ELSCs are and correspond to pluripotent embryonic-like stem cells, PPELSCs, as originally designated and described in the instant patent Application USSN 09/668,508 and its priority applications. The pluripotent embryonic-like stem cells/epiblast-like stem cells have not been found to differentiate to sperm or ova. PPELSCs/ELSCs are not totipotent – they cannot form gametes.

7. At the time of filing of the instant Application and its priority applications, an antibody recognizing spermatogonia (DHTuAG1) was used to test for the appearance of spermatogonia in cultures of ELSCs incubated with our general induction medium. However, no positive staining was seen in the assays. This same antibody has been used to test for the appearance of spermatogonia in general induction medium-induced differentiating cultures of BLSCs. Positive staining was observed in BLSC cultures, demonstrating the ability of BLSCs to form male gametes. No staining was observed in cultures of differentiating ELSCs, GLEctoSCs, GLMesoSCs, or GLEndoSCs with the anti-spermatogonia antibody under the same conditions. Thus, in our hands, PPELSCs/ELSCs were not totipotent and do not give rise to male gametes. Please see Phenotypic Bioassay as Assessed by Antibody Microarray ELICA and Table 1, attached hereto as Exhibit C.

8. I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that the statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under §10001 of Title 18 of the United States code and that such willful false statements may jeopardize the validity of the Application for any patent issuing thereon.

Date: 6-30-04


Henry E. Young

RESEARCH CURRICULUM VITAE

NAME: Henry Edward Young, Ph.D.

TITLE: Professor of Anatomy
ADDRESS: Division of Basic Medical Sciences,
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Professor of Pediatrics
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DATE OF BIRTH: December 5, 1951

PLACE OF BIRTH: Dayton, Ohio, USA

MARITAL STATUS: Married, 1976 - Valerie
Children: Katherine (09-5-89)

HIGHER EDUCATION:

Ohio State University, Columbus, OH - B.S., Biology, 1974

University of Arkansas, Fayetteville, AR - M.S., Zoology, 1977

Master's Thesis: Limb Regeneration in the Adult Salamander, *Ambystoma annulatum*
Cope 1889 (Amphibia: Ambystomatidae). (Dr. Claudia F. Bailey)

Texas Tech University, Lubbock, TX - Ph.D., Anatomy, 1983

Ph.D. Thesis: A Temporal Examination of Glycoconjugates During the Initiation
Phase of Limb Regeneration in Adult *Ambystoma*. (Dr. Roger R.
Markwald)

Case Western Reserve University, Cleveland, OH - Postdoctoral Fellow, Glycoconjugate
Biochemistry (Dr. Arnold I. Caplan), 1983-1987

DISCOVERED Skeletal muscle morphogenetic protein, Scar inhibitory factor
Adult germ layer lineage mesodermal stem cells (GL-MesoSCs)
Adult epiblast-like stem cells (ELSCs)
Adult blastomere-like stem cells (BLSCs)

ACADEMIC HONORS AND AWARDS:

- 1974 Scholarship, University of Arkansas, Fayetteville, AR.
- 1976 Award for Graduate Student Teaching Excellence, University of Arkansas, Fayetteville, AR.
- 1979 Bio-Medical Research Grant, Texas Tech University, Lubbock, TX.
- 1980-1981 Scholarship, Texas Tech University, Lubbock, TX.
- 1981 Sigma Xi Research Grant-in-Aid, Texas Tech University, Lubbock, TX.
- 1983-1985 Muscular Dystrophy Association of America Postdoctoral Fellowship, Case Western Reserve University, Cleveland, OH.
- 1985-1987 NIH Postdoctoral Fellowship in Developmental Biology, Case Western Reserve University, Cleveland, OH.
- 1993 **Invited Seminar:** "Mesenchymal Stem Cells, A Potential Donor Source for Human Tissue Transplantation"; The Children's Hospital - Boston/Harvard Medical School, Boston, MA, March 18-19, 1993, Mercer University School of Medicine, Macon, GA.
- 1993 **Hooding Award:** "In Recognition of Excellence in Quality Medical Education and Promotion of Student Biomedical Research". Presented by Mercer University School of Medicine Graduating Class of 1993, June 5, 1993.
- 1993 **Certificate of Merit:** "Awarded to Henry Edward Young for Distinguished Service to the International Scientific Community, International Biographical Centre, Cambridge, England, August, 1993.
- 1994 **Hooding Award:** "In Recognition of Excellence in Quality Medical Education and Promotion of Student Biomedical Research". Presented by Mercer University School of Medicine Graduating Class of 1994, June 4, 1994.
- 1995 Dictionary of International Bibliography, 23rd Ed.
- 1996 Men of Achievement, 17th Ed.
- 1997-pres Strathmore's WHO's Who in Medicine and Healthcare, Marquis Publishing Co., New Providence, NJ

- 1997 **Gender Equity Award**, "For promoting a gender-fair environment for the education and training of women physicians and assuring equal opportunity for women and men to study and practice medicine". Presented by the American Medical Women's Association, Inc., Mercer University School of Medicine, October, 1997.
- 1997 **Invited Presentation**: "Clinical Application of Bioactive Factors and Stem Cells in Wound Healing and Regeneration", November 12, 1997, Stem Cells and Tissue Engineering, University of Pittsburgh Medical Center, Pittsburgh, PA.
- 1999 **Invited Presentation**: "Mesenchymal Stem Cells and Tissue Engineering", April 24, 1999, Cardiovascular Tissue Engineering, The Medical University of South Carolina, Charleston, SC.
- 1999 **Invited Co-chairmanship**: "Cells for Cardiovascular Tissue Engineering: Origin, Isolation, and Differentiation", April 24, 1999, Cardiovascular Tissue Engineering, The Medical University of South Carolina, Charleston, SC.
- 1999 **Invited Presentation**: "Postnatal Pluripotent Stem Cells", October 3-5, 1999, 2nd Annual Tissue Engineering/Regenerative Healing/Stem Cell Biology Conference, Pittsburgh, PA.
- 1999 **Invited Presentation**: "Adult-Derived Pluripotent Stem Cells Showing Bone and Cartilage Regeneration", Nov. 30-Dec. 3, 1999, 4th Annual International Conference on Cellular Engineering, Nara, Japan.
- 2000 **Invited Presentation**: "Stem Cell Differentiation", June 1-2, 2000, Invited Workshop on "Stem Cell Biology: Potential and Promise" of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institute of Aging (NIA), National Institutes of Health, Bethesda, MD.
- 2000 **Invited Presentation**: "Fibrodysplasia Ossificans, When Stem Cell Repair Goes Awry", November 4, 2000, The Joseph Leidy Lecture in Cell Biology, presented at The Third International Symposium on Fibrodysplasia Ossificans Progressiva (FOP), November 2-5, 2000, Philadelphia, PA.
- 2001-pres **Invited Participation**: The Science Advisory Board, a group of life scientists from around the world who convene electronically to comment on emerging technologies.
- 2001 **Newspaper Article**: "Adult Stem Cells", Macon Telegraph, Macon, GA, December 3, 2001.
- 2002 **National Public Radio**: "Adult Pluripotent Stem Cells" All Things Considered, January 24, 2002.

- 2002 **Invited Presentation:** “Potential of Reserve Postnatal Pluripotent Stem Cells for Tissue Engineering”, June 6-8, 2002, presented at the Stem Cell Conference for Tolerance and Tissue Engineering, Snowbird, Utah.
- 2002 **Invited Participation:** NIH, NIAMS Study Section, “Basic and Applied Stem Cell Research for Arthritis and Musculoskeletal Diseases”, August 30, 2002, Bethesda, MD.
- 2004 **Profiled in:** “Enter the Matrix. More than just filling space, the extracellular matrix affects human health.” R. Lewis, *The Scientist* 18:28-29, 2004.
- 2005 **Humanism in Medicine Award:** The Arnold P. Gold Foundation *Leonard Tow Humanism in Medicine Award*, the individual judged to be exemplary in their compassion and sensitivity in the delivery of care (education) to their patients (students) as well as respect for their colleagues, May 8, 2005.
- 2005 **Inductee:** Arnold P. Gold Foundation - **Gold Humanism Honor Society**, May 8, 2005.
- 2005 **Invited Participation:** NIH/NINDS Study Section, "Centers of Excellence in Translational Human Stem Cell Research", July 14-15, 2005, Bethesda, MD.
- 2006 **Invited Presentation:** “Adult stem cells”, American Association of Anatomists mini symposium on Stem Cells and Regenerative Medicine, Experimental Biology, April 1-4, 2006

RESEARCH AND PROFESSIONAL EXPERIENCE:

- 1975-1977 Graduate Student Teaching Assistant, Department of Zoology, University of Arkansas, Fayetteville, AR.
- 1978-1983 Graduate Student Teaching Assistant, Department of Anatomy, Texas Tech University Health Sciences Center, Lubbock, TX.
- 1983-1985 Postdoctoral Fellow, Muscular Dystrophy Association of America, Department of Biology, Case Western Reserve University, Cleveland, OH.
- 1985-1987 Postdoctoral Fellow, NIH Fellowship in Developmental Biology, Department of Biology, Case Western Reserve University, Cleveland, OH.
- 1987-1988 Instructor, Department of Biochemistry, Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL.
- 1988-1995 Assistant Professor of Anatomy, Division of Basic Medical Science, Mercer University School of Medicine, Macon, GA.

1988-Pres	Director of Embryology, Division of Basic Medical Science, Mercer University School of Medicine, Macon, GA.
1988-1993	Co-Director of Histology, Division of Basic Medical Science, Mercer University School of Medicine, Macon, GA.
1988-1994	Adjunct Assistant Professor of Surgery, Department of Surgery, Mercer University School of Medicine, Macon, GA.
1988-1989	Interim Director of Surgical Research, Department of Surgery, Mercer University School of Medicine, Macon, GA.
1989-1994	Assistant Director of Surgical Research, Department of Surgery, Mercer University School of Medicine, Macon, GA.
1995-Pres	Associate Professor of Anatomy, with Tenure, Division of Basic Medical Science, Mercer University School of Medicine, Macon, GA.
1995-Pres	Adjunct Associate Professor of Pediatrics, Department of Pediatrics, Mercer University School of Medicine, Macon, GA.
2004-Pres	Full Professor of Anatomy, with Tenure, Division of Basic Medical Science, Mercer University School of Medicine, Macon, GA.
2004-Pres	Adjunct Full Professor of Pediatrics, Department of Pediatrics, Mercer University School of Medicine, Macon, GA.

MEMBERSHIPS IN PROFESSIONAL SOCIETIES

American Association of Anatomists
 American Society for Cell Biology
 Federation of American Societies for Experimental Biology
 Society for In Vitro Biology
 The Wound Healing Society
 Society for Experimental Biology and Medicine
 Society of Regenerative Medicine and Stem Cell Biology
 Gold Humanism Honor Society

PUBLICATIONS

Peer Reviewed

1. Young, H.E.: Epidermal ridge formation during limb regeneration in the adult salamander, *Ambystoma annulatum*. *Proceedings of the Arkansas Academy of Science*, 31:107-109, 1977.
2. Young, H.E.: Anomalies during limb regeneration in the adult salamander, *Ambystoma annulatum*. *Proceedings of the Arkansas Academy of Science*, 31:110- 111, 1977.
3. Young, H.E., Bailey, C.F., Dalley, B.K.: Environmental conditions prerequisite for complete limb regeneration in the postmetamorphic adult land-phase salamander, *Ambystoma*. *Anatomical Record*, 206:289-294, 1983.
4. Young, H.E., Bailey, C.F., Dalley, B.K.: Gross morphological analysis of limb regeneration in postmetamorphic adult *Ambystoma*. *Anatomical Record*, 206:295-306, 1983.
5. Young, H.E., Bailey, C.F., Markwald, R.R., Dalley, B.K.: Histological analysis of limb regeneration in postmetamorphic adult *Ambystoma*. *Anatomical Record*, 212:183-194, 1985.
6. Young, H.E., Carrino, D.A., Caplan, A.I.: Initial characterization of small proteoglycans synthesized by embryonic chick leg muscle-associated connective tissues. *Connective Tissue Research*, 17:99-118, 1988.
7. Young, H.E., Dalley, B.K., Markwald, R.R.: Effect of selected denervations on glycoconjugate composition and tissue morphology during the initiation phase of limb regeneration in adult *Ambystoma*. *Anatomical Record*, 223:223-230, 1989.
8. Young, H.E., Dalley, B.K., Markwald, R.R.: Glycoconjugates in normal wound tissue matrices during the initiation phase of limb regeneration in adult *Ambystoma*. *Anatomical Record*, 223:231-241, 1989.
9. Young, H.E., Young, V.E., Caplan, A.I.: Comparison of fixatives for maximal retention of glycoconjugates for autoradiography, including use of sodium sulfate to release unincorporated radiolabeled [35S]sulfate. *Journal of Histochemistry and Cytochemistry*, 37:223-228, 1989.
10. Young, H.E., Carrino, D.A., Caplan, A.I.: Histochemical analysis of newly synthesized and resident sulfated glycosaminoglycans during musculogenesis in the embryonic chick leg. *Journal of Morphology*, 201:85-103, 1989.
11. Young, H.E., Carrino, D.A., Caplan, A.I.: Changes in synthesis of sulfated glycoconjugates during muscle development, maturation, and aging in embryonic to senescent CBF-1 mouse. *Mechanisms of Ageing and Development*, 53:179-193, 1990.

12. Young, H.E., Morrison, D.C., Martin, J.D., and Lucas, P.A.: Cryopreservation of embryonic chick myogenic lineage-committed stem cells. *Journal of Tissue Culture Methods*, 13:275-284, 1991.
13. Shoptaw, J.H., Bowerman, S., Young, H.E. Young, Lucas, P.A.: Use of gelfoam as a substrate for osteogenic cells of marrow. *Surgical Forum XLII*:537-538, 1991.
14. Bowerman, S.G., Taylor, S.S., Putnam, L., Young, H.E., Lucas, P.A.: Transforming growth factor-b (TGF-b) stimulates chondrogenesis in cultured embryonic mesenchymal cells. *Surgical Forum XLII*:535-536, 1991.
15. Young, H.E., Sippel, J., Putnam, L.S., Lucas, P.A., Morrison, D.C.: Enzyme-linked immuno-culture assay. *Journal of Tissue Culture Methods*, 14:31-36, 1992.
16. Young, H.E., Ceballos, E.M., Smith, J.C., Lucas, P.A., Morrison, D.C.: Isolation of embryonic chick myosatellite and pluripotent stem cells. *Journal of Tissue Culture Methods*, 14:85-92, 1992.
17. Young, H.E., Ceballos, E.M., Smith, J.C., Mancini, M.L., Wright, R.P., Ragan, B.L., Bushell, I., Lucas, P.A.: Pluripotent mesenchymal stem cells reside within avian connective tissue matrices. *In Vitro Cellular & Developmental Biology*, 29A:723-736, 1993.
18. Pate, D.W., S.S. Southerland, D.A. Grande, H.E. Young, P.A. Lucas: Isolation and differentiation of mesenchymal stem cells from rabbit muscle. *Surgical Forum*, XLIV:587-589, 1993.
19. Rogers, J.J., Adkison, L.R., Black, A.C., Jr., Lucas, P.A., Young, H.E.: Differentiation factors induce expression of muscle, fat, cartilage, and bone in a clone of mouse pluripotent mesenchymal stem cells. *The American Surgeon* 61(3):1-6, 1995.
20. Young, H.E., Mancini, M.L., Wright, R.P., Smith, J.C., Black, A.C., Jr., Reagan, C.R., Lucas, P.A. Mesenchymal stem cells reside within the connective tissues of many organs. *Developmental Dynamics* 202:137-144, 1995.
21. Black, A.C., Jr., Goolsby, L.W., Cohen, G.A., Young, H.E. Effects of prenatal ethanol exposure on the hippocampal neurochemistry of albino rats at 90 days of postnatal age. *Am. J. Obstet. Gynecol.* 173:514-519, 1995.
22. Lucas, P.A., Calcutt, A.F., Southerland, S.S., Warejcka, D., Young, H.E.: A population of cells resident within embryonic and newborn rat skeletal muscle is capable of differentiating into multiple mesodermal phenotypes. *Wound Repair and Regeneration* 3:457-468, 1995.
23. Warejcka, D.J., Harvey, R., Taylor, B.J., Young, H.E., Lucas, P.A. A population of cells isolated from rat heart capable of differentiating into several mesodermal phenotypes. *J. Surg. Res.* 62:233-242, 1996.

24. Lucas, P.A., Warejcka, D.J., Zhang, L-M., Newman, W.H., Young, H.E.: Effect of rat mesenchymal stem cells on the development of abdominal adhesions after surgery. *J. Surg. Res.* 62:229-232, 1996.
25. Lucas, P.A., Warejcka, D.J., Young, H.E., Lee, B.Y. Formation of abdominal adhesions is inhibited by antibodies to transforming growth factor-beta1. *J. Surg. Res.* 65:135-138, 1996.
26. Dixon, K., Murphy, R.W., Southerland, S.S., Young, H.E., Dalton, M.L., Lucas, P.A.: Recombinant human bone morphogenetic proteins-2 and 4 (rhBMP-2 and rhBMP-4) induce several mesenchymal phenotypes in culture. *Wound Repair and Regeneration* 4:374-380, 1996.
27. Young, H.E., Wright, R.P., Mancini, M.L., Lucas, P.A., Reagan, C.R., Black, A.C., Jr.: Bioactive factors affect proliferation and phenotypic expression in pluripotent and progenitor mesenchymal stem cells. *Wound Repair and Regeneration* 6(1):65-75, 1998.
28. Young, H.E., Rogers, J.J., Adkison, L.R., Lucas, P.A., Black, A.C., Jr. Muscle morphogenetic protein induces myogenic gene expression in Swiss-3T3 cells. *Wound Rep Reg* 6(6):543-554, 1998.
29. Young, H.E., Steele, T., Bray, R.A., Detmer, K., Blake, L.W., Lucas, P.A., Black, A.C., Jr. Human progenitor and pluripotent cells display cell surface cluster differentiation markers CD10, CD13, CD56, and MHC Class-I. *Proc. Soc. Exp. Biol. Med.* 221:63-71, 1999.
30. Young, H.E., Duplaa, C., Young, T.M., Floyd, J.A., Reeves, M.L., Davis, K.H., Mancini, G.J., Eaton, M.E., Hill, J.D., Thomas, K., Austin, T., Edwards, C., Cuzzourt, J., Parikh, A., Groom, J., Hudson, J., Black, A.C., Jr. Clonogenic analysis reveals reserve stem cells in postnatal mammals. I. Pluripotent mesenchymal stem cells. *Anat. Rec.* 263:350-360, 2001.
31. Young, H.E., Steele, T., Bray, R.A., Hudson, J., Floyd, J.A., Hawkins, K., Thomas, K., Austin, T., Edwards, C., Cuzzourt, J., Duenzl, M., Lucas, P.A., Black, A.C. Jr. Human reserve pluripotent mesenchymal stem cells are present in the connective tissues of skeletal muscle and dermis derived from fetal, adult, and geriatric donors. *Anat. Rec.* 264:51-62, 2001.
32. Romero-Ramos M, Vourc'h P, Young HE, Lucas PA, Wu Y, Chivatakarn O, Zaman R, Dunkelman N, El-Kalay MA, Chesselet M-F Neuronal differentiation of stem cells isolated from adult muscle. *J Neurosci Res* 69:894-907, 2002.
33. Young HE. Existence of reserve quiescent stem cells in adults, from amphibians to humans. *Curr Top Microbiol Immunol.* 280:71-109, 2004.
34. Young HE, Black Jr AC. Adult stem cells. *Anat. Rec.* 276A:75-102, 2004.
35. Young HE, Duplaa C, Romero-Ramos M, Chesselet M-F, Vourc'h P, Yost MJ, Ericson K, Terracio L, Asahara T, Masuda H, Tamura-Ninomiya S, Detmer K, Bray RA, Steele TA, Hixson D, El-Kalay M, Tobin BW, Russ RD, Horst MN, Floyd JA, Henson NL, Hawkins KC, Groom J, Parikh A, Blake L, Bland LJ, Thompson AJ, Kirincich A, Moreau C, Hudson J, Bowyer III FP,

Lin TJ, Black Jr AC. Adult reserve stem cells and their potential for tissue engineering. *Cell Biochem Biophys*, 40(1):1-80, 2004a.

36. Young HE, Duplaa C, Yost MJ, Henson NL, Floyd JA, Detmer K, Thompson AJ, Powell SW, Gamblin TC, Kizziah K, Holland BH, Boev A, Van de Water JM, Godbee DC, S. Jackson, M. Rimando, Edwards CR, Wu E, Cawley C, Edwards PD, Macgregor A, Bozof R, Thompson TM, Petro Jr GJ, Shelton HM, McCampbell BL, Mills JC, Flynt FL, Steele TA, Kearney M, Kirincich-Greathead A, Hardy W, Young PR, Amin AV, Williams RS, Horton MM, McGuinn S, Hawkins KC, Ericson K, Terracio L, Moreau C, Hixson D, Tobin BW, Hudson J, Bowyer III FP, Black Jr AC. Clonogenic analysis reveals reserve stem cells in postnatal mammals. II. Pluripotent epiblastic-like stem cells. *Anat. Rec.* 277A:178-203, 2004b.

37. Vourc'h P, Romero-Ramos M, Chivatakarn O, Young HE, Lucas PA, El-Kalay M, Chesselet M-F. Isolation and characterization with neurogenic potential from adult skeletal muscle. *Biochemical and Biophysical Research Communications* 317:893-901, 2004.

38. Seruya M, Shah A, Pedrotty D, du Laney T, Melgiri R, McKee JA, Young HE, Niklason LE. Clonal Population of adult stem cells: life span and differentiation potential. *Cell Transplant* 13:93-101, 2004

39. Vourc'h P, Lacar B, Mignon L, Lucas PA, Young HE, Chesselet MF. Effect of neurturin on multipotent cells isolated from the adult skeletal muscle. *Biochem Biophys Res Commun* 332:215-223, 2005.

40. Henson NL, Heaton ML, Holland BH, Hawkins KC, Rawlings B, Eanes E, Bozof R, Powell S, Grau R, Fortney J, Peebles B, Kumar D, Yoon JI, Godby K, Collins JA, Sood R, Bowyer 3rd FP, Black Jr AC, Young HE. Karyotypic analysis of adult pluripotent stem cells. *Histology and Histopathology*, 20: 769-784, 2005.

41. Mignon L, Vourc'h P, Romero-Ramos M, Osztermann P, Young HE, Lucas PA, Chesselet MF. Transplantation of multipotent cells extracted from adult skeletal muscles into the adult subventricular zone. *J Cell Neurol* 491:96-108, 2005.

42. Young HE, Duplaa C, Katz R, Thompson T, Hawkins KC, Boev AN, Henson NL, Heaton M, Sood R, Ashley D, Stout C, Morgan JH, Uchakin PN, Rimando M, Long GF, Thomas C, Yoon JI, Park JE, Hunt DJ, Walsh NM, Davis JC, Lightner JE, Hutchings AM, Murphy ML, Boswell E, McAbee JA, Gray BM, Piskurich J, Blake L, Collins JA, Moreau C, Hixson D, Bowyer FP, Black AC Jr. Adult-derived stem cells and their potential for tissue repair and molecular medicine. *J Cell Molec Med* 9:753-769, 2005.

43. Young HE, Black AC Jr. Adult-derived stem cells. *Minerva Biotechnologica* 17:55-63, 2005b.

44. Vourc'h P, Mignon L, Lucas PA, Young HE, Chesselet MF. Cells isolated from adult skeletal muscle express markers of differentiated neurons after transplantation into the adult hippocampus. (In press).

Book Chapters

1. Young, H.E.: Limb Regeneration in the Adult Salamander, *Ambystoma annulatum* Cope 1889 (Amphibia: Ambystomatidae). University of Arkansas Library Press, copyright -1977.
2. Young, H.E.: A Temporal Examination of Glycoconjugates During the Initiation Phase of Limb Reneration in Adult *Ambystoma*. Texas Tech University Library Press, copyright - 1983.
3. Young, H.E., Dalley, B.K., Markwald, R.R.: Identification of hyaluronate within peripheral nervous tissue matrices during limb regeneration. Edited by Coates, P.W., Markwald, R.R., Kenny, A.D., Alan R. Liss, Inc., New York. In: *Developing and Regenerating Vertebrate Nervous Systems, Neurology and Neurobiology*, 6:175-183, 1983.
4. Young, H.E. Pluripotent stem cells. Edited by M.A. Brown and S. Neufeld, Cambridge Healthtech Institute Press, Newton Upper Falls, MA. In: *Second Annual Symposium on Tissue Engineering / Regenerative Healing / Stem Cell Biology*, 469-530, 1999.
5. Young, H.E. Stem cells and tissue engineering. In: *Gene Therapy in Orthopaedic and Sports Medicine*, J. Huard and F.H. Fu, eds., Springer-Verlag New York, Inc., Chap. 9, pg. 143-173, 2000.
6. Young HE and Black AC Jr. Differentiation potential of adult stem cells. In: *Contemporary Endocrinology: Stem Cells in Endocrinology*, L.B. Lester, ed., The Humana Press Inc., Totowa, NJ. Chap. 4, p. 67-92, 2005a.

ABSTRACTS

1. Young, H.E., Dalley, B.K.: Regional distribution of the matrix components during the early stages of limb regeneration in the adult salamander. *Anatomical Record*, 193:285(A), 1979.
2. Young, H.E., Dalley, B.K.: Study of the glycosaminoglycans of the extracellular matrix underlying the regenerating epidermis during wound healing. *Anatomical Record*, 199:758(A), 1981.
3. Young, H.E., Dalley, B.K., Markwald, R.R.: The interaction of glycosaminoglycans (GAG) and nervous tissue regeneration in adult *Ambystoma*. *Anatomical Record*, 205:202(A), 1983.
4. Young, H.E., Caplan, A.I.: Analysis of proteoglycans synthesized by muscle-associated tissues during muscle development in the embryonic chick leg. *Anatomical Record*, 214:148(A), 1986.
5. Young, H.E. and Lucas, P.A.: Factor(s) derived from demineralized bone matrix stimulates myogenesis in vitro and in vivo. *Anatomical Record*, 220:107A, 1988.
6. Getelis, S., Block, J.A., Inerot, S.E., Young, H.E., Schajowicz, F., Glant, T., Kimura, J.H.: Clonal analysis of human chondrosarcomas. *Transactions Orthopedic Research Society*, 1989.

7. Young, H.E., Morrison, D.C., Sealy, W.: Insulin-like growth factor-1 stimulates proliferation in myogenic lineage-committed and uncommitted pluripotent stem cells. *Journal of Cellular Biochemistry Supplement*, 14E:255, 1990.
8. Young, H.E., Morrison, D.C.: Endogenous growth actor affects myogenic differentiation in uncommitted pluripotent and lineage-committed stem cells. *Anatomical Record*, 226(4):113A, 1990.
9. Elgin, J., Morrison, D.C., Lucas, P.A., Young, H.E.: Cryopreservation of stem cells. *FASEB Journal*, 5(5):A1174, 1991.
10. Ragan, B.L., Breving, R.E., Taylor, B.J., Morrison, D.C., Lucas, P.A., Young, H.E.: Enzyme-linked immuno-culture assay (ELICA), a sensitive measure of phenotypic expression. *FASEB Journal*, 5(5):A1174, 1991.
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62. Detmer, K. and H.E. Young Homeobox gene expression in mammalian skin. Program of the 9th International Conference of the International Society of Differentiation (ISD), Inc., Development, Cell Differentiation, and Cancer, Pisa, Italy, September 28 to October 2, 1996.
63. Black, A.C., Jr., Lin, T.-J., and Young, H.E. Model of the Fetal Alcohol Syndrome. *FASEB J.* 11(3):A384, 1997.
64. Young, H.E., Bray, R., Steele, T.A., Lucas, P.A., Blake, L.W., Detmer, K., Black, A.C., Jr. Human mesenchymal stem cells display cell surface cluster differentiation markers. Program of Cambridge Healthtech Institute's Symposium on Tissue Engineering and Regenerative Healing, Pittsburgh, PA, September 27-29, 1998.
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67. Black, A.C., Jr., Lin, T.-J., Young, H.E. Evaluation of the effects of administration of ethanol in a liquid diet to pregnant Sprague-Dawley rats on the hippocampal neurochemistry of their progeny. The Mercer University Health Sciences Research Conference. April 27, 2000.
68. Young HE, Duplaa C, Bray RA, Detmer K, Floyd JA, Hawkins KC, Groom J, Parikh A, Blake L, Duenzl M, Bland LJ, Thompson AJ, Hixson D, Hudson J, Bowyer III FP, Lin T-J, Black Jr AC. Reserve Pluripotent Stem Cells Resembling Embryonic Stem Cells are Present in

Postnatal Mammals, Including Humans. MUSM 2nd Southeastern Family Medicine and Primary Care Research Conference, April 12-13, 2002.

69. Young, H.E. Potential of Reserve Postnatal Pluripotent Stem Cells for Tissue Engineering. Stem Cell Therapy and Autoimmune Diseases Conference, June 6-8, 2002, Snowbird, UT.

70. Young HE, Yost MJ, Henson NL, Floyd JA, Bowyer III FP, Black Jr AC. Adult pluripotent stem cells assist in the repair of heart muscle after tissue damage, Mercer University Health Sciences Research Conference, March 4, 2004.

71. Floyd JA, Henson NL, Hawkins KC, Davis JW, Detmer K, Thompson AJ, Bowyer III FP, Black Jr AC, Young, HE. Adult pluripotent stem cells, Mercer University Health Sciences Research Conference, March 4, 2004.

72. Jackson S, Rimando M, Henson NL, Floyd JA, Bowyer III FP, Black Jr AC, Young, HE. Growth factor-induced proliferation of adult pluripotent stem cells, Mercer University Health Sciences Research Conference, March 4, 2004.

73. Henson NL, Heaton ML, Floyd JA, Bowyer III FP, Black Jr AC, Young, HE. Karyotypic analysis of adult pluripotent stem cells, Mercer University Health Sciences Research Conference, March 4, 2004.

74. Hawkins KC, Davis JW, Henson NL, Floyd JA, Tobin BW, Bowyer III FP, Black Jr AC, Young, HE. Induced pancreatic islets from adult pluripotent stem cells, Mercer University Health Sciences Research Conference, March 4, 2004.

75. Katz RM, Young HE, Thompson TL. Stem cell implantation into lesioned striatum. Induced pancreatic islets from adult pluripotent stem cells, Mercer University Health Sciences Research Conference, March 4, 2004.

76. Young HE, Black Jr AC. Isolation and Cultivation of Adult Stem Cells, and Their Potential for Use in Treating Human Disease. GTCbios Conference, International Conference on Stem Cells Research and Therapeutics, San Diego, CA, April 11-12, 2005.

United States Patents

1. Muscle Morphogenetic Protein and Use Thereof: a compound that stimulates the restoration of skeletal muscle in vivo and induces the differentiation of stem cells into a myogenic phenotype in vitro. United States Patent Number: 5,328,695, July 12, 1994.

2. Pluripotent Mesenchymal Stem Cells and Methods of Use Thereof: a cell having the capability of extended self-renewal and the ability to form multiple mesodermal lineages in vivo and in vitro. United States Patent Number: 5,827,735, October 27, 1998.
3. Pluripotent Embryonic-Like Stem Cells, Compositions, Methods, and Uses Thereof: a cell having the capability of extended self-renewal and the ability to form multiple ectodermal, mesodermal and endodermal lineages in vivo and in vitro. United States Patent Pending.
4. Adult-Derived Blastomere-Like Stem Cells, Compositions, Methods and Uses Thereof: a cell having the capability of extended self-renewal and the ability to form any cell type of the conceptus in vivo and in vitro. United States Patent Pending.
5. Serum-Free Defined Reagents for the Isolation, Cultivation, Cryopreservation, and Purification of Blastomere-Like Stem Cells for Diagnostic and Human Clinical Applications: Compositions and Methods. United States Patent Pending.
6. Serum-Free Defined Reagents for the Isolation, Cultivation, Purification, and Cryopreservation of Epiblast-Like Stem Cells for Diagnostic and Human Clinical Applications: Compositions and Methods. United States Patent Pending.

Scientific Founder and Consultant – Biotechnology companies

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| 1994-2004 | Scientific Founder, MorphoGen Pharmaceuticals Inc., 9855 Towne Center Drive, San Diego, CA 92121 |
| 2004 - present | Consultant, CYBIOS LLC, [Acquired the assets of MorphoGen in 2004], 9855 Towne Center Drive, San Diego, CA 92121 (858) 558-3100 [Terry M. Ryusaki, CEO] |
| 2004 - present | Moraga Biotechnology Corporation, 1061 Moraga Drive, Suite 100, Los Angeles, CA (310) 440-0374 [John F. Wong, Ph.D., CEO] |

Invited Presentations

1. "Factor(s) Derived from Demineralized Bone Matrix Influence Tissue Replacement and Repair", October 28, 1988, Department of Surgery, Medical Center of Central Georgia, Macon
2. "Bone Factors Affect Skeletal Muscle Repair", June 26, 1990, Continuing education sponsored by Proctor & Gamble, Cincinnati, Ohio.
3. "Biology of Scar Formation", Surgical Residents' Basic Science Conference - Applied Surgical Anatomy, February 12, 1991, Medical Center of Central Georgia, Macon
4. "Pluripotent Stem Cells, A Model System for Phenotypic Expression". May 14, 1991, Mercer Day of Science, Mercer University School of Medicine, Macon, GA.
5. "Uncommitted Pluripotent Stem Cells, A Model for Cellular Differentiation", August 13, 1991, Continuing education sponsored by La Jolla Cancer Research Foundation, La Jolla, CA.

6. "Factor Induced In Vivo Skeletal Muscle Repair", August 14, 1991, Continuing education sponsored by La Jolla Cancer Research Foundation, La Jolla, CA.
7. "Development and Structure of Cartilage and Bone", August 27, 1991, Surgery Dept., Medical Center of Central Georgia, Macon, GA.
8. "Cartilage and Bone", September 23, 1991, Continuing education sponsored by Proctor & Gamble Co., Cincinnati, OH
9. "Effects of Bioactive Factors on Mesenchymal Stem Cells", January 28, 1992, Department of Surgery, Medical Center of Central Georgia, Macon, GA.
10. "Effects of Muscle Morphogenetic Protein In Vitro"; February 4, 1992, Continuing education sponsored by Creative Biomolecules, Boston, MA.
11. "Effects of Fibroblast Inhibitory Factor In Vitro and In Vivo"; February 10, 1992, Continuing education sponsored by Dragonfly Foundation for Research and Development, Columbus, OH.
12. "Learning gross anatomy in a problem-based basic science curriculum organized by organ systems." Program of the Southern Group on Educational Affairs of the Association of American Medical Colleges Meeting, Mercer University School of Medicine, Macon, GA, March 26-28, 1992.
13. "Learning embryology and histology in a problem-based basic science curriculum organized by organ systems." Program of the Southern Group on Educational Affairs of the Association of American Medical Colleges Meeting, Mercer University School of Medicine, Macon, GA, March 26-28, 1992.
14. "Mesenchymal Stem Cells and Factors that Influence their Differentiation"; May 21-23, 1992, Continuing education sponsored by Advanced Tissue Sciences, San Diego, CA.
15. "Mesenchymal Stem Cells and Factors that Influence their Differentiation"; July 9-11, 1992, Continuing education sponsored by Genetics Institute, Boston, MA.
16. "Mesenchymal Stem Cells, A Potential Donor Source for Human Tissue Transplantations"; March 18-19, 1993, Continuing education sponsored by The Children's Hospital - Boston/Harvard Medical School, Boston, MA.
17. "Pluripotent Mesenchymal Stem Cells, A Potential Donor Source for Human Tissue Transplantations"; May 4, 1993; Continuing education sponsored by The Castle Group, Ltd., New York, NY.
18. "Stem Cells", September 14, 1993, Internal Medicine Resident Education, The Medical Center of Central Georgia, Macon, GA.

19. "Congenital Megacolon: Hirschsprung's Disease, A congenital defect of neural crest cell migration and invasion", August 30, 1994, Pediatric Grand Rounds, The Medical Center of Central Georgia, Macon, GA.
20. "Tissue Engineering", March 28, 1995, Continuing education sponsored by Sey Group International, Atlanta, GA.
21. "Neuroblastoma, An Embryonic Tumor of Neural Crest Origin", April 25, 1995, Pediatric Grand Rounds, The Medical Center of Central Georgia, Macon, GA.
22. "Mesenchymal Stem Cells and Regeneration", June 6, 1995, Continuing education sponsored by Department of Surgery, Carolinas Medical Center, Charlotte, NC.
23. "Muscle Morphogenetic Protein and Mesenchymal Stem Cells", August 31, 1995, Continuing education sponsored by MorphoGen Pharmaceuticals, New York, NY.
24. "Mesenchymal Stem Cells: Potential Donor Source for Tissue Restoration", 05-28-96, Research Seminar Series, BioMedical Research Committee, Mercer University School of Medicine, Macon, GA.
25. "Mesenchymal Stem Cells", August 6, 1996, Continuing education sponsored by Genetics Institute, Cambridge, MA.
26. "Mesenchymal Stem Cells, Muscle Morphogenetic Protein, and Scar Inhibitory Factor", August 6, 1996, Continuing education sponsored by Creative Biomolecules, Hopkinton, MA.
27. "Stem Cells and Factors That Influence Their Differentiation", November 11, 1997, Continuing education sponsored by Department of Plastic and Reconstructive Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA.
28. "Clinical Application of Bioactive Factors and Stem Cells in Wound Healing and Regeneration", Clinical Symposium, November 12, 1997, University of Pittsburgh Medical Center, Pittsburgh, PA.
29. "Isolation of Human Mesenchymal Stem Cells Using Flow Cytometry", January 16, 1998, Continuing education sponsored by Cytotherapeutics, Palo Alto, CA.
30. "Isolation of Human Mesenchymal Stem Cells Using Flow Cytometry", March 9, 1998, Continuing education sponsored by Osiris Therapeutics, Inc., Baltimore, MD.
31. "Stem Cells and Tissue Engineering", December 3, 1998, Continuing education sponsored by United States Surgical Corporation, Hartford, CT.
32. "Mesenchymal Stem Cells and Tissue Engineering", April 24, 1999, Workshop on Cardiovascular Tissue Engineering, The Medical University of South Carolina, Charleston, SC.

33. Co-Chairman of Session "Cells for Cardiovascular Tissue Engineering: Origin, Isolation, and Differentiation", April 24, 1999, Cardiovascular Tissue Engineering, Continuing education sponsored by The Medical University of South Carolina, Charleston, SC.
34. "Pluripotent Stem Cells", August 20, 1999, Continuing education sponsored by Department of Anesthesiology/ Biomedical Engineering, Duke University, Durham, NC.
35. "Pluripotent Stem Cells Exist in Postnatal Mammals", September 1, 1999, Continuing education sponsored by Department of Cell Biology and Anatomy, Medical University of South Carolina, Charleston, SC.
36. "Postnatal Pluripotent Stem Cells", October 4, 1999, Continuing education sponsored by Department of Plastic and Reconstructive Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA.
37. "Postnatal Pluripotent Stem Cells", October 3-5, 1999, Cambridge Healthtech Institute's 2nd Annual Tissue Engineering/Regenerative Healing/Stem Cell Biology Conference, Pittsburgh, PA.
38. "Skeletal muscle regeneration using pluripotent stem cells", Nov. 29, 1999, Continuing education sponsored by Department of Orthopedics, Nara Medical University, Kashihara City, Nara 634-8522, JAPAN
39. "Adult-Derived Pluripotent Stem Cells Showing Bone and Cartilage Regeneration", Nov. 30 to Dec. 3, 1999, 4th Annual International Conference on Cellular Engineering, Nara, Japan, Dec. 3, 1999.
40. Chairperson of Session "Osteogenic Potential of Bone Marrow-Derived Osteoblasts", Nov. 30 to Dec. 3, 1999, 4th Annual International Conference on Cellular Engineering, Nara, Japan, Dec. 3, 1999.
41. "Reserve Stem Cells and Tissue Restoration", Division of Basic Medical Science, MUSM, Dec. 7, 1999.
42. "Reserve Stem Cells and Tissue Restoration, from Amphibians to Humans", Continuing education sponsored by Herman B Wells Center for Pediatric Research, Indiana University School of Medicine, Indianapolis, IN, December 13, 1999.
43. "Reserve Stem Cells and Tissue Restoration, from Amphibians to Humans", Continuing education sponsored by Trillium VC, New York, NY, in Macon, GA, December 14, 1999.
44. "Reserve Stem Cells and Tissue Restoration, from Amphibians to Humans", Continuing education sponsored by Sulzer-Innotech, Austin, TX, in Macon, GA, December 15, 1999.

45. "Reserve Stem Cells and Tissue Restoration, from Amphibians to Humans", Continuing education sponsored by Department of Neurology, UCLA School of medicine, Los Angeles, CA, January 25, 2000.
46. "Science and Art in Culturing Pluripotent Stem Cells", Direct a four day training session in stem cell culture, Department of Neurology, UCLA School of Medicine, Los Angeles, CA, January 26-29, 2000.
47. "Adult-Derived Pluripotent Stem Cells Showing Bone and Cartilage Regeneration", April 12, 2000, Continuing education sponsored by Department of Orthopaedics, Rhode Island Hospital, Brown University, Providence, RI.
48. "Developmental Potential of Reserve Postnatal Pluripotent Stem Cells", April 12, 2000, Continuing education sponsored by Department of Orthopaedics, Rhode Island Hospital, Brown University, Providence, RI.
49. "Developmental Potential of Reserve Postnatal Pluripotent Stem Cells", May 8, 2000, Continuing education sponsored by Cardiovascular Research and Medicine, St. Elizabeth's Medical Center, Boston, MA.
50. "Science and Art in Culturing Pluripotent Stem Cells", Direct a four day training session in stem cell culture, May 8-11, 2000, Continuing education sponsored by Cardiovascular Research and Medicine, St. Elizabeth's Medical Center, Boston, MA.
51. "Developmental Potential of Reserve Postnatal Pluripotent Stem Cells", May 18, 2000, Continuing education for Clonetics/ BioWhittaker Corporation, San Diego, CA at Mercer University School of Medicine, Macon, Georgia.
52. "Developmental Potential of Reserve Postnatal Pluripotent Stem Cells", May 23, 2000, Continuing education sponsored by Georgia Institute of Technology, Atlanta, GA.
53. "Stem Cell Differentiation", June 1-2, 2000, Invited Presentation at Workshop on "Stem Cell Biology: Potential and Promise" of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institute of Aging (NIA), National Institutes of Health, Bethesda, MD.
54. "Developmental Potential of Reserve Postnatal Pluripotent Stem Cells", July 14, 2000, Continuing education sponsored by Department of Biomedical Engineering, Duke University, Durham, NC.
55. "Science and Art in Culturing Pluripotent Stem Cells", Direct a seven day training session in stem cell culture, July 13-19, 2000, Department of Biomedical Engineering, Duke University, Durham, NC.

56. "Developmental Potential of Reserve Postnatal Pluripotent Stem Cells", July 27, 2000, Continuing education sponsored by Department of Pharmacology, Emory University, Atlanta, GA.
57. "Developmental Potential of Reserve Postnatal Pluripotent Stem Cells", August 8, 2000, Continuing education sponsored by Division of Metabolic Bone Diseases and Molecular Orthopaedics, The University of Pennsylvania School of Medicine, Philadelphia, PA.
58. "Developmental Potential of Reserve Postnatal Pluripotent Stem Cells", September 8, 2000, Continuing education sponsored by Herman B Wells Center for Pediatric Research, Indiana University School of Medicine, Indianapolis, IN.
59. "Science and Art in Culturing Pluripotent Stem Cells", September 7-12, 2000, Direct a six day training session in stem cell culture, Herman B Wells Center for Pediatric Research, Indiana University School of Medicine, Indianapolis, IN.
60. "Developmental Potential of Reserve Postnatal Pluripotent Stem Cells", September 14, 2000, Department of Surgery and Developmental Biology and Anatomy, University of South Carolina School of Medicine, Columbia, South Carolina.
61. "Science and Art in Culturing Pluripotent Stem Cells", September 14-18, 2000, Direct a six day training session in stem cell culture, Department of Surgery and Developmental Biology and Anatomy, University of South Carolina School of Medicine, Columbia, South Carolina.
62. "Reserve Pluripotent Epiblastic-Like Stem Cells are Present in Adult Humans", September 27, 2000, Continuing education sponsored by Stevens Group Incorporated, Little Rock, Arkansas.
63. "Fibrodysplasia Ossificans, When Stem Cell Repair Goes Awry", November 3, 2000, The Joseph Leidy Lecture in Cell Biology, presented at The Third International Symposium on Fibrodysplasia Ossificans Progressiva (FOP), November 2-5, 2000, Philadelphia, PA.
64. "Developmental Potential of Reserve Postnatal Pluripotent Stem Cells", November 13, 2000, Continuing education sponsored by Department of Surgery and Developmental Biology and Anatomy, University of South Carolina School of Medicine, Columbia, South Carolina.
65. "Science and Art in Culturing Pluripotent Stem Cells", November 11-16, 2000, Continuing education sponsored by Department of Surgery and Developmental Biology and Anatomy, University of South Carolina School of Medicine, Columbia, South Carolina.
66. "Art and Science in Culturing Pluripotent Stem Cells", December 8-15, 2000. Direct a seven day training session in pluripotent stem cell isolation and cultivation, MorphoGen Pharmaceuticals, Inc., San Diego, CA.

67. "Developmental Potential of Reserve Postnatal Pluripotent Stem Cells", March 1, 2001, Continuing education sponsored by Department of Biology, University of Arkansas, Fayetteville, AR.
68. "Use of Pluripotent Stem Cells for Cardiac Repair", March 15, 2001, Continuing education sponsored by Department of Surgery and Developmental Biology and Anatomy, University of South Carolina School of Medicine, Columbia, South Carolina.
69. "Use of Pluripotent Stem Cells to Bioengineer Blood Vessels for Vascular Grafting", March 16, 2001, Continuing education sponsored by Department of Biomedical Engineering, Duke University, Durham, NC.
70. "Use of Postnatal Pluripotent Stem Cells as Augmentation for Pancreatic Islet Transplantation", April 25, 2001, Continuing education sponsored by Diabetes Research Institute, University of Miami School of Medicine, Miami, FL.
71. "Developmental Potential of Reserve Postnatal Pluripotent Stem Cells", May 2, 2001, Continuing education sponsored by Dept. of Immunology and Microbiology, School of Medicine, University of North Carolina, Chapel Hill, NC.
72. "Potential of Reserve Postnatal Pluripotent Stem Cells for Tissue Engineering", May 8, 2001, Continuing education sponsored by Department of Biomedical Engineering, Drexel University, Philadelphia, PA.
73. "Potential of Reserve Postnatal Pluripotent Stem Cells for Tissue Engineering", May 29, 2001, Continuing education sponsored by Department of Surgery, Emory University School of Medicine, Atlanta, GA.
74. "Potential of Reserve Postnatal Pluripotent Stem Cells for Tissue Engineering", June 19, 2001, Continuing education sponsored by Medtronics Corp., Minneapolis, MN.
75. "Isolation and Cultivation of Pluripotent Stem Cells", June 23, 2001, MorphoGen Pharmaceuticals, Inc., San Diego, CA.
76. "Art and Science in Culturing Pluripotent Stem Cells", June 22-26, 2001. Direct a five day workshop in pluripotent stem cell isolation and cultivation, MorphoGen Pharmaceuticals, Inc., San Diego, CA.
77. "Postnatal Skeletal Muscle Contains Pluripotent Stem Cells", July 14-19, 2001, Continuing education sponsored by FASEB Summer Research Conference, Omni Tucson, Tucson, AZ.
78. "Adult Pluripotent Stem Cells for Tissue Engineering", July 30, 2001, Continuing education sponsored by AIG Global Investment Company in Atlanta, GA.

79. "Adult Pluripotent Stem Cells as a Delivery Platform for Gene Therapy", August 14-19, 2001, Continuing education sponsored by Chromos Molecular Systems, Inc., Burnaby, British Columbia, Canada.
80. "Art and Science in Culturing Adult Human Pluripotent Stem Cells", August 14-19, 2001, Direct a five day training session in pluripotent stem cell isolation and cultivation, Chromos Molecular Systems, Inc., Burnaby, British Columbia, Canada.
81. "Art and Science in Culturing Pluripotent Stem Cells", August 20-24. Direct a five day training session in pluripotent stem cell isolation and cultivation, for Drexel University, Philadelphia, PA at Mercer University School of Medicine, Macon, GA.
82. "Plasticity of Adult Stem Cells for Tissue Engineering", September 11, 2001, Continuing education sponsored by Tennille Rotary Club, Tennille, GA.
83. "Plasticity of Adult Stem Cells for Tissue Engineering", September 26, 2001, Continuing education sponsored by University Research and Health Affairs Office of University Relations, Mercer University, Macon, GA.
84. "Plasticity of Adult Stem Cells for Tissue Engineering", October 7, 2001, Continuing education sponsored by St. Andrews Presbyterian Church, Macon, GA.
85. "Reserve Pluripotent Stem Cells, Building Blocks for Tissue Restoration", November 27, 2001, Division of Basic Medical Sciences, Mercer University School of Medicine, Macon, GA..
86. "Stem Cells, Building Blocks for Tissue Replacement", February 19, 2002, Pediatric Grand Rounds, MCCG, Macon, GA.
87. "Reserve Pluripotent Stem Cells Resembling Embryonic Stem Cells are Present in Postnatal Mammals, Including Humans", April 12-13, 2002, Poster Presentation, MUSM 2nd Southeastern Family Medicine and Primary Care Research Conference, Savannah, GA.
88. "Potential of Reserve Postnatal Pluripotent Stem Cells for Tissue Engineering", June 6-8 2002, Continuing education sponsored by Stem Cell Therapy and Autoimmune Diseases Conference, Snowbird, UT.
89. "Potential of Reserve Postnatal Pluripotent Stem Cells for Tissue Engineering", September 15-16, 2002, Continuing education sponsored by Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, GA.
90. "Potential of Reserve Postnatal Pluripotent Stem Cells for Tissue Engineering", September 24, 2002, Continuing education sponsored by Cardiovascular Research Institute, Moorehouse School of Medicine, Atlanta, GA.

91. "Potential of Reserve Postnatal Pluripotent Stem Cells for Tissue Engineering", November 15, 2002, for Department of Nursing, Georgia College and State University, Milledgeville, GA at Mercer University School of Medicine, Macon, GA.
92. "Stem Cells, Potential for Tissue Restoration", November 18, 2002, Wesleyan College, Macon, GA.
93. "Stem Cells", September 30, 2003, Cell Dynamics LLC, Atlanta, GA.
94. "Adult Stem Cells and Tissue Repair", October 29, 2003, MUSM, Macon, GA.
95. "Adult pluripotent stem cells assist in the repair of heart muscle after tissue damage", [poster presentation], March 4, 2004, Mercer University Health Sciences Research Conference, Medical Center of Central Georgia, Macon, GA.
96. "Adult stem cells and tissue repair", December 18, 2004, for Terry Ryusaki, CEO, Cybios Inc., San Diego, CA at MUSM.
97. "Adult derived pluripotent stem cells & their rolls in tissue engineering", January 13, 2005, Scientific Research at Mercer University, Willet Science Center, Rm 221.
98. "Adult stem cells: cell sorting procedures", January 18, 2005, Cybios LLC., San Diego, CA.
99. "Adult stem cells and tissue repair", January 19, 2005, Cybios LLC., San Diego, CA.
100. "Adult precursor cells – detailed isolation procedures", January 20, 2005, Cybios LLC., San Diego, CA.
101. "Adult stem cells and embryonic stem cells: isolation, characterization, function: in vitro and in vivo", January 21, 2005, Cybios LLC., San Diego, CA.
102. "Adult stem cells and tissue repair", February 14, 2005, Olympus Corporation, Los Angeles, CA.
103. "Adult stem cells and tissue repair", February 15, 2005, City of Hope, Los Angeles, CA.
104. "Adult stem cells and their potential for treating human diseases", February 15, 2005, City of Hope, Los Angeles, CA.
105. "Adult stem cells and aging", February 15, 2005, City of Hope, Los Angeles, CA.
106. "Adult stem cells and their potential for treating type-I diabetes", February 15, 2005, City of Hope, Los Angeles, CA.
107. "Adult stem cells and tissue repair", February 15, 2005, Keck Graduate Institute, Los Angeles, CA.

108. "Adult stem cells versus embryonic stem cells: isolation, characterization, and function: in vitro and in vivo", February 16, 2005, The Archer School., Los Angeles, CA.
109. "Adult-derived blastomere-like stem cells and their potential for high throughput screening for drug discovery", February 16, 2005, Moraga Biotechnology Corp., Los Angeles, CA.
110. "Adult-derived blastomere-like stem cells and their potential for high throughput screening for drug discovery", February 16, 2005, Aurora Discovery, San Diego, CA.
111. "Adult-derived blastomere-like stem cells and tissue repair", February 16, 2005, Novel Bioventures, San Diego, CA.
112. "Adult-derived blastomere-like stem cells and the use of serum free-defined reagents for their growth", February 17, 2005, Cellerant, Los Angeles, CA.
113. "Adult-derived blastomere-like stem cells as delivery vehicles for gene therapy", February 17, 2005, City of Hope, Los Angeles, CA.
114. "Adult stem cells and their potential for treating type-I diabetes", February 17, 2005, City of Hope, Los Angeles, CA.
115. "Adult-derived blastomere-like stem cells as a tolerization agent for organ transplantation", February 17, 2005, City of Hope, Los Angeles, CA.
116. "Adult-derived stem cells versus embryonic stem cells: state of the art", February 17, 2005, City of Hope, Los Angeles, CA.
117. "Adult stem cells and tissue repair", April 11, 2005, Novel Bioventures, San Diego, CA.
118. "Isolation and cultivation of adult stem cells, and their potential for use in treating human disease", April 11, 2005, Burnham Institute, San Diego, CA.
119. "Adult stem cells and tissue repair", April 12, 2005, Vet-Stem, Regenerative Veterinary Medicine, San Diego, CA.
120. "Isolation and cultivation of adult stem cells, and their potential for use in treating human disease", April 12, 2005, Lifeline Cell Technologies, San Diego, CA.
121. "Adult stem cells and tissue repair", April 15, 2005, Wesleyan College, Macon, GA.
122. "Adult Stem Cells and Tissue Repair", May 5, 2005, to Gary Fuji, President and CEO, Molecular Express, Los Angeles, CA.
123. "Adult stem cells and tissue repair", October 19, 2005, for Dr. Michelle Greene, Stem Cell Biology Group, Chemicon, Temecula, CA at MUSM.

124. "Adult stem cells and tissue repair", October 26, 2005, for Dr. Vi Chu, Stem Cell Biology Group, Chemicon, Temecula, CA
125. "Adult stem cells and tissue repair", November 9, 2005, for Dr. Deepa Arora, Department of Biology, Fort Valley State University
126. "Adult stem cells and tissue repair", November 15, 2005, for Dr. Stephen Navrin, Stem Cell Biology Group, Synthecon, Houston, TX
127. "Adult stem cells and tissue repair", January 18, 2006, JHM, Inc., Camilla, GA
128. "Adult stem cells and tissue repair", January 26, 2006, Stemedica, San Diego, CA
129. "Anti-Differentiation Factor versus Leukemia Inhibitory Factor, which works best with stem cells", February 7, 2006, Dr. Herbert Hermann, PAA Laboratories GmbH, Unterm Bornrain 2, 35091 Coelbe, Germany
130. "Adult stem cells and medical therapies", February 26, 2006, for Dr. George McCommon, DVM, Fort Valley State University.
131. "Adult stem cells and medical therapies", March 2, 2006, Department of Veterinary Medicine, Fort Valley State University, Fort Valley, GA
132. "Adult stem cells and medical therapies", March 9, 2006, for Jason Limnios, Department of Obstetrics & Gynecology, University of Adelaide, Adelaide, Australia
133. "Adult stem cells and medical therapies", March 16, 2006, for third year medical students from Kanasawa, Japan
134. "Adult Stem Cells", March 21, 2006, Specialty Plants Biotechnology, Agricultural Research Station, Fort Valley State University, Fort Valley, GA
135. "Adult stem cells", American Association of Anatomists mini symposium on Stem Cells and Regenerative Medicine, Experimental Biology, April 1-4, 2006, (invited).
136. "Adult stem cells and medical therapies", April 18, 2006, for Dr. Scott Burger, Advanced Cell and Gene Therapy, Chapel Hill, NC.
137. "Adult stem cells and medical therapies", May 13, 2006, for Dr. Marius Rataczjak and research group, Institute for Stem Cell Biology, University of Louisville, Louisville, KY.
138. "Adult stem cells and medical therapies", May 25, 2006, Coca-Cola Research Group, Atlanta, GA
139. "Isolation of taste bud cells", May 25, 2006, Coca-Cola Research Group, Atlanta, GA

140. "Adult stem cells and translational research", June 4, 2006, American Society for Clinical Oncology, for Dr. Benny Zee, The Chinese University of Hong Kong, Atlanta, GA
141. "The use of decellularized pancreatic matrices for the culture of pancreatic islets of Langerhans", June 4, 2006, American Society for Clinical Oncology, for Dr. Benny Zee, The Chinese University of Hong Kong, Atlanta, GA
142. "Adult stem cells and translational research", June 4, 2006, American Society for Clinical Oncology, for Mr. Richard Howard, EVP – Strategic Alliances, Bridgetech Holdings International, Inc., Solona Beach, CA, Atlanta, GA
143. "The use of decellularized pancreatic matrices for the culture of pancreatic islets of Langerhans", June 4, 2006, American Society for Clinical Oncology, for Mr. Richard Howard, EVP – Strategic Alliances, Bridgetech Holdings International, Inc., Solona Beach, CA, Atlanta, GA
144. "Adult stem cells and translational research", June 4, 2006, American Society for Clinical Oncology, for Dr. Anthony Maida, Braxis Pharmaceuticals, Atlanta, GA
145. "The use of decellularized pancreatic matrices for the culture of pancreatic islets of Langerhans", June 4, 2006, American Society for Clinical Oncology, for Dr. Anthony Maida, Braxis Pharmaceuticals, Atlanta, GA

Research and Program Support (Awarded)

- | | |
|-----------|---|
| 1989-1990 | "Endogenous Signaling Factors Effect Stem Cell Differentiation", Principal Investigator, Rubye Ryle Smith Charitable Trust, \$ 8,000 direct/\$0 indirect.
"Adult Stem Cells", Principal Investigator, Henry O. Young Estate Trust, \$5,000 direct/\$0 indirect. |
| 1990-1992 | "Isolation of Myogenic Factors from Bone Matrix", Principal Investigator, MCGG Clinical MedCen Foundation, 90-92, \$ 28,640 direct/\$0 indirect. |
| 1990-1991 | "Endogenous Signaling Factors Effect Stem Cell Differentiation", Principal Investigator, Rubye Ryle Smith Charitable Trust, \$ 4,100 direct/\$0 indirect.
"Isolation of Myogenic Signaling Factors from Bone", Principal Investigator, MCGG Clinical MedCen Foundation, \$ 9,956 direct/\$0 indirect.
"Adult Stem Cells", Principal Investigator, Henry O. Young Estate Trust, \$5,000 direct/\$0 indirect. |
| 1991-1992 | "Endogenous Signaling Factors Effect Stem Cell Differentiation", Principal Investigator, Rubye Ryle Smith Charitable Trust, \$ 3,000 direct/\$0 indirect. |

"In Vitro Activities of Bone Morphogenetic Factors and Other Proteins", Co-Investigator, Procter & Gamble, \$ 10,000 direct/\$0 indirect.

"Further Purification of Muscle Morphogenetic Protein (MMP)", Principal Investigator, MCCG Clinical MedCen Foundation, \$ 27,133 direct/\$0 indirect.

"Adult Stem Cells", Principal Investigator, Henry O. Young Estate Trust, \$5,000 direct/0\$ indirect.

"Are insulin and insulin-like growth factors myogenic agents for pluripotent stem cells" advisor to Jennifer C. Smith, Sigma Xi Research Grant-in-Aid, \$ 350 direct/\$0 indirect.

"Do pluripotent stem cells reside within skeletal muscle-associated connective tissues?", advisor to Elizenda M. Ceballos, Sigma Xi Research Grant-in-Aid, \$ 350 direct/\$0 indirect.

1992-1993 "Effects of Bio-Active Factors on Stem Cell Growth and Differentiation", Principal Investigator, Rubye Ryle Smith Charitable Trust, \$ 3,000 direct/\$0 indirect.

"Isolation, Purification, and Testing of Muscle Morphogenetic Protein", Principal Investigator, MCCG Clinical MedCen Foundation, \$ 21,306 direct/\$0 indirect.

"Adult Stem Cells", Principal Investigator, Henry O. Young Estate Trust, \$2,500 direct/0\$ indirect.

"Efficacy Study of Muscle Morphogenetic Protein, Co-Investigator, Genetics Institute, \$11,000 direct/\$0 indirect.

"Avian Mesenchymal Stem Cells and Enzyme-Linked Immuno-Culture Assay", Principal Investigator, Genetics Institute, \$ 12,000 direct/\$0 indirect.

"Isolation of Human Mesenchymal Stem Cells", Co-Investigator, Advanced Tissue Sciences, \$ 9,000 direct/\$0 indirect.

"Gross Quantification of Adhesion Formation in Post Laparotomy Introduction of Adhesion Inhibitory Substance in Controlled Release Vehicles", co-advisor with Dr. Paul Lucas, Cancer Research Awards for Medical Students to Robert Breving, American Cancer Society Georgia Division, \$500 direct/\$0 indirect.

"Histologic Quantification of Adhesion Formation in Post Laparotomy Introduction of Adhesion Inhibitory Substance in Controlled Release Vehicles", co-advisor with Dr. Paul Lucas, Cancer Research Awards for Medical Students to Patrick Culligan, American Cancer Society Georgia Division, \$500 direct/\$0 indirect.

"Isolation of Putative Mesenchymal Stem Cells from Embryonic Chick Heart", advisor to Matthew L. Mancini, Cancer Research Awards for Medical Students, American Cancer Society Georgia Division, \$500 direct/\$0 indirect.

"Isolation of Putative Mesenchymal Stem Cells from Embryonic Chick Skin", advisor to Robert P. Wright, Cancer Research Awards for Medical Students, American Cancer Society Georgia Division, \$500 direct/\$0 indirect.

1993-1994 "Effects of Bio-Active Factors on Stem Cell Growth and Differentiation",

Principal Investigator, Rubye Ryle Smith Charitable Trust, \$ 3,000 direct/\$0 indirect.

"Use of Stem Cells for Treatment of Myopathies", Co-Investigator, Clinical MedCen Foundation, \$ 84,920 direct/\$0 indirect.

"Adult Stem Cells", Principal Investigator, Henry O. Young Estate Trust, \$2,500 direct/0\$ indirect.

"The Effect of TNF-a on Mesenchymal Stem Cell Differentiation", co-advisor. with Dr Leeper-Woodford to Edrea Jones, Cancer Research Awards for Medical Students, American Cancer Society Georgia Division, \$ 500 direct/\$0 indirect.

1994-1995 "Effects of Bio-Active Factors on Stem Cell Growth and Differentiation", Principal Investigator, Rubye Ryle Smith Charitable Trust, 10/94-9/95, \$2,250 direct/\$0 indirect.

"Adult Stem Cells", Principal Investigator, Henry O. Young Estate Trust, \$2,500 direct/0\$ indirect.

1995-1996 "Ethanol and Acetaldehyde Affect Stem Cell Development", Principal Investigator, Medcen Foundation, \$20,000 direct/\$0 indirect.

"Effects of Bio-Active Factors on Stem Cell Growth and Differentiation", Principal Investigator, Rubye Ryle Smith Charitable Trust, \$2,250 direct/\$0 indirect.

"Adult Stem Cells", Principal Investigator, Henry O. Young Estate Trust, \$2,500 direct/0\$ indirect.

1996-2004 "Tissue Engineering", Principal Investigator; MorphoGen Pharmaceuticals, Inc., \$272,730 direct/ \$27,270 indirect.

1996-1997 "Effects of Bio-Active Factors on Stem Cell Growth and Differentiation", Principal Investigator, Rubye Ryle Smith Charitable Trust, \$ 2,250 direct/\$0 indirect.

"Adult Stem Cells", Principal Investigator, Henry O. Young Estate Trust, \$2,500 direct/0\$ indirect.

1997-1998 "Effects of Bio-Active Factors on Stem Cell Growth and Differentiation", Principal Investigator, Rubye Ryle Smith Charitable Trust, \$ 2,150 direct/\$0 indirect.

"Adult Stem Cells", Principal Investigator, Lucille M. and Henry O. Young Estate Trust, \$2,500 direct/0\$ indirect.

- 1998-1999 "Effects of Bio-Active Factors on Stem Cell Growth and Differentiation", Principal Investigator, Rubye Ryle Smith, Charitable Trust, \$ 2,150 direct/\$0 indirect.
"Adult Stem Cells", Principal Investigator, Lucille M. and Henry O. Young Estate Trust, \$2,500 direct/0\$ indirect.
- 1999-2000 "Human Mesenchymal Stem Cells for Hematopoietic Therapies", Principal Investigator, MedCen Foundation Education Award. \$20,000 direct/\$0 indirect.
"Adult Stem Cells", Principal Investigator, Lucille M. and Henry O. Young Estate Trust, \$2,500 direct/0\$ indirect.
- 2000-2001 "Pluripotent Stem Cells for Juvenile Diabetic Therapy", Principal Investigator, MedCen Foundation Education Award, \$20,000 direct/\$0 indirect
" Pluripotent Stem Cells and Hematopoiesis ", Principal Investigator, MedCen Foundation Education Award. \$20,000 (direct), \$0 (indirect), \$20,000 (total).
"Adult Stem Cells", Principal Investigator, Lucille M. and Henry O. Young Estate Trust, \$2,500 direct/0\$ indirect.
- 2001-2002 "Pluripotent Stem Cells for Juvenile Diabetic Therapy", Principal Investigator MedCen. Foundation Education Award \$20,000 (direct), \$0 (indirect), \$20,000 (total).
" Pluripotent Stem Cells and Hematopoiesis ", Principal Investigator, MedCen Foundation Education Award. \$20,000 (direct), \$0 (indirect), \$20,000 (total).
"Effects of Bio-Active Factors on Stem Cell Growth and Differentiation", Principal Investigator, Rubye Ryle Smith Charitable Trust. \$6,250 (direct), \$0 (indirect), \$6,250 (total).
"Adult Stem Cells", Principal Investigator, Lucille M. and Henry O. Young Estate Trust, \$2,500 direct/0\$ indirect.
- 2002-2003 "Function of Pancreatic Islets Derived from Adult Pluripotent Stem Cells", Principal Investigator, MedCen Foundation Education Award. \$20,000 (direct), \$0 (indirect), \$20,000 (total).
"Effects of Bio-Active Factors on Stem Cell Growth and Differentiation", Principal Investigator, Rubye Ryle Smith Charitable Trust. \$6,250 (direct), \$0 (indirect), \$6,250 (total).
"Adult Stem Cells", Principal Investigator, Lucille M. and Henry O. Young Estate Trust, \$2,500 direct/0\$ indirect.
- 2003-2004 "Effects of Bio-Active Factors on Stem Cell Growth and Differentiation", Principal Investigator, Rubye Ryle Smith Charitable Trust. \$6,250 (direct), \$0 (indirect), \$6,250 (total).

“Adult Stem Cells”, Principal Investigator, Lucille M. and Henry O. Young Estate Trust, \$2,500 direct/0\$ indirect.

- 2004-2005 "Effects of Bio-Active Factors on Stem Cell Growth and Differentiation",
Principal Investigator, Rubye Ryle Smith Charitable Trust. \$6,250 (direct), \$0 (indirect), \$6,250 (total).
“Adult Stem Cells”, Principal Investigator, Lucille M. and Henry O. Young Estate Trust, \$2,500 direct/0\$ indirect.
“Use of Adult Pluripotent Stem Cells in Parkinson’s Disease”,
Principal Investigator, MedCen Foundation Education Award. \$20,000 (direct), \$0 (indirect), \$20,000 (total).
- 2004-2006 “Characterization of adult stem cells in reproductive organs”, Co-PI, MedCen Foundation, \$36,000 (direct), \$0 (indirect), \$36,000 (total).
- 2005-2006 “Expansion of Pancreatic Beta Islets utilizing a decellularized pancreatic matrix as a stimulus for auto/epithelial cell division or maturation and utilization for transplantation”, Co-PI, JHM, Inc. \$50,000 (direct), \$0 (indirect), \$50,000 (total)
“Expansion of Pancreatic Beta Islets utilizing a decellularized pancreatic matrix”,
Co-PI, MedCen Foundation, \$17,000 (direct), \$0 (indirect), \$17,000 (total)
"Effects of Bio-Active Factors on Stem Cell Growth and Differentiation",
Principal Investigator, Rubye Ryle Smith Charitable Trust. \$6,250 (direct), \$0 (indirect), \$6,250 (total).
“Adult Stem Cells”, Principal Investigator, Lucille M. and Henry O. Young Estate Trust, \$2,500 direct/0\$ indirect

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Reviewer for Scientific Journals

Cell and Tissue Research
Anatomical Record
Wound Repair and Regeneration
Journal of Histopathology
IN VITRO Cellular & Developmental Biology – Animal
Histology & Histopathology
Differentiation

Adult-derived stem cells

H. E. YOUNG^{1,2}, A. C. BLACK JR^{1,3}

Four categories of cells have been previously identified in postnatal mammals, including humans. These categories are differentiated cells, cell- and tissue-committed progenitor cells, germ layer lineage-committed stem cells and lineage-uncommitted pluripotent stem cells. All 4 categories of cells display normal karyotypes. Differentiated cells are variable in size. They form the physiological functional components of the tissue. Progenitor cells are also variable in size and are the immediate precursors of differentiated cells. Germ layer lineage stem cells range in size from 10-20 μm and can be induced to form multiple cell types belonging to their respective ectodermal, mesodermal, and endodermal embryological lineages. Pluripotent stem cells range in size from 6-8 μm and will form somatic cell types from all 3 primary germ layer lineages, but will not form the sperm or ova. Differentiated cells, progenitor cells, and germ layer lineage stem cells are contact inhibited at confluence. In contrast, pluripotent stem cells can form multiple layers of cells post confluence. Differentiated cells and progenitor cells demonstrate a finite life span before replicative senescence and cell death occur. Both germ layer lineage stem cells and pluripotent stem cells are telomerase positive and display extensive capabilities for self-renewal. Recently, a 5th category of cell was discovered in postnatal tissues. These putative stem cells are less than 1 μm in size. They demonstrate a normal karyotype. These cells are the immediate precursors to the pluripotent stem cells. They can form all somatic cells of the body and spermatogonia. These cells have shown extensive capabilities for self-renewal. They will form multiple layers of cells post confluence. Shared and unique characteristics will be discussed for these 5 categories of adult-derived cells.

KEY WORDS: Mammals - Humans, adult-derived, stem cells - Germ layer lineage - Progenitor.

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Adult-derived cells

Postnatal tissues contain differentiated cells and precursor cells. The precursor cells exist within adult differentiated tissues as a community of cells dispersed throughout the tissue, rather than as discrete populations of cells within selected tissue types. Adult-derived precursor cells have been segregated into 3 categories based on their expressed differentiation potential. These 3 categories are pluripotent stem cells, germ layer lineage stem cells, and progenitor cells.¹⁻³

The 1st category of precursor cells consists of a single pluripotent stem cell with the potential to form all the somatic cells of the body. This cell displays a normal karyotype. The pluripotent stem cell has a unique pattern of cell surface markers. It is telomerase positive and has demonstrated extended capabilities for self-renewal far exceeding the preprogrammed replicative clock progenitor cells and differentiated cells of rodent and human origin (Table I).^{2,6} The pluripotent stem cell does not exhibit contact inhibition at confluence, but continues to proliferate to form multiple confluent layers of cells *in vitro*.^{2,5} This pluripotent stem cell is responsive to any lineage-induction agent

TABLE I.—Five categories of cells located within adult tissues.

Characteristics	DCs	PCs	GLLSCs	ELSCs	BLSCs
Size	Variable	Variable	10-20 μ m	6-8 μ m	< 1 μ m
Chromosome number					
— Rat	42*	42	42	42	42
— Human	46	46	46	46	42 nyrd
Viability within tissue post mortem at 4°C					
— Rat	3-5 h	24 h	3 days	5 days	7+ days
— Human	3-5 h	24 h	3 days	5 days	7+ days
Cell Release from solid tissue					
— Explant	—	±	+	+	+
— Mincing	—	+	+	+	+
— Enzymatic	+	+	+	+	+
Presence in:					
— Blood	+	+	+	+	+
— Bone marrow	+	+	+	+	+
Percentage within solid tissues	50	45	4	0.95	0.05
Location within solid tissues	Through-out tissue	Through-out tissue	Within connective tissue compartments	Within connective tissue compartments	Within connective tissue compartments
Positive CD marker profile (Human)	Cell Specific*	Cell Specific*	CD10, CD13 CD90, MHC-I	CD10, CD66e	CD66e
Negative CD marker profile (Human)	Cell Specific*	Cell Specific*	CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD9, CD11b, CD11c, CD14, CD15, CD16, CD18, CD19, CD20, CD22, CD23, CD24, CD25, CD31, CD33, CD34*, CD36, CD38, CD41, CD42b, CD45, CD49d, CD55, CD56*, CD57, CD59, CD61, CD62E, CD65, CD68, CD69, CD71, CD79, CD83, CD95, CD105, CD117, CD123, CD135, CD166, Glycophorin-A, HLA-DRII, FMC-7, Annexin-V, and LIN	CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD9, CD11b, CD11c, CD13, CD14, CD15, CD16, CD18, CD19, CD20, CD22, CD23, CD24, CD25, CD31, CD33, CD34, CD36, CD38, CD41, CD42b, CD45, CD49d, CD55, CD56, CD57, CD59, CD61, CD62E, CD65, CD68, CD69, CD71, CD79, CD83, CD90, CD105, CD105, CD117, CD123, CD135, CD166, Glycophorin-A, MHC-I, HLA-DRII, FMC-7, Annexin-V, and LIN	CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD9, CD10, CD11b, CD11c, CD13, CD14, CD15, CD16, CD18, CD19, CD20, CD22, CD23, CD24, CD25, CD31, CD33, CD34, CD36, CD38, CD41, CD42b, CD45, CD49d, CD55, CD56, CD57, CD59, CD61, CD62E, CD65, CD68, CD69, CD71, CD79, CD83, CD90, CD105, CD105, CD117, CD123, CD135, CD166, Glycophorin-A, MHC-I, HLA-DRII, FMC-7, Annexin-V, and LIN

Continued Table I

Table 1 continued.

Characteristics	DCs	PCs	GLSCs	ELSCs	BLSCs
Cloned from a single cell (Rat)	na	+	A ₂ A ₂ β	Sci-40β	Sci-9β
Cryopreservation					
— DMSO	Ultra-pure	Ultra-pure	Ultra-pure	Ultra-pure	Ultra-pure
— Conc	10%	10%	7.5%	7.5%	7.5%
— Temp	Liq N ₂	Liq N ₂	-70°±5 °C	-80°±5 °C	-80°±5 °C
— Freeze Proc	Flash	Flash	Slow	Slow	Slow
— Thaw Proc	Fast to ambient	Fast to ambient	Fast to ambient	Fast to ambient	Fast to ambient
— % Recovery	>95%	>95%	>98%	>98%	>98%
Substrates:					
— Make their own	+	+	-	-	-
— Adherent	+	+	+	+	+
— Ca ⁺⁺ dep	+	+	+	+	+
— RGD dep	+	+	+	+	-
— Susp cult	+	+	-	-	+
Cultivation using Serum-Free Defined Reagents (SFD):					
— SFD-PC	+	+	-	-	-
— SFD-GLSC	+	+	+	-	-
— SFD-ELSC	+	+	+	+	-
— SFD-BLSC	+	+	+	+	+
Response to a proliferation agent ¹⁸	+	+	+	+	+
Proliferation Rate (Rat and Human)	Days to months	Days to weeks	18-24 h	12-14 h	nyd
Growth at Confluence	Contact inhibited	Contact inhibited	Contact inhibited	Multiple confluent layers	Multiple confluent layers
Replicative potential					
— Rat	8-10	8-10	Extensive	Extensive	Extensive
— Human	50	50-70	Extensive	Extensive	nyd
Cell doublings to date w/o loss of differentiation potential					
— Rat (clones)	na	nyd	>400	>300	>300
— Human	na	50	>690	>400	nyd
Activity in SFD medium w/o inhib-	Functional	Quiescent	Quiescent	Quiescent	Quiescent
LIF activity preconfluent	na	Induction inhibition	Induction inhibition	Induction inhibition	nyd
LIF activity postconfluent	na	na	na	No effect	nyd
Dependent variable to LIF	na	Absolute cell numbers	Absolute cell numbers	Absolute cell numbers	nyd
Concentration of LIF	na	2 000 U/mL	2 000 U/mL	2 000 U/mL	nyd
ADF activity preconfluent	na	Induction inhibition	Induction inhibition	Induction inhibition	No effect
ADF activity postconfluent	na	na	na	Induction inhibition	No effect
Dependent variable to ADF	na	Inductive factor concentration	Inductive factor concentration	Inductive factor concentration	No effect
Concentration of ADF	na	2 U/mL	2 U/mL	2 U/mL	No effect
Response to progression agent(s)	-	+	-	-	-
Response to inductive agent(s)	-	-	+	+	+
Immediate Precursor Cell for:	na	DCs	PCs	GLSCs	ELSCs
Cell types formed	na	Cell-specific	Ectodermal, mesodermal, & endodermal lineage cells	All somatic cells only, will NOT form gametes	All somatic cells and spermatogonia

Continued Table 1

Table 1 continued.

Characteristics	DCs	PCs	GLSCs	ELSCs	BLSCs
Telomerase activity					
— Rat (clones)	na	na	+	+	nyd
— Human	na	nyd	nyd	nyd	nyd
Oct 3/4 Expression					
— Rat (clones)	na	na	—	+	nyd
— Human	na	nyd	nyd	nyd	nyd
Activity <i>in vivo</i>	Functional	Quiescent or reparative	Quiescent or reparative	Quiescent or reparative	Quiescent or reparative
Studies with repair models	na	na	Bone, articular cart, skeletal muscle, bone marrow reconstitution	Parkinson's disease, Myocardial infarction, Type-I diabetes mellitus	Parkinson's disease, Myocardial infarction, Type-I diabetes mellitus, Bone marrow reconstitution, Infertility

DCs: differentiated cells; PCs: progenitor cells; GLSCs: germ layer lineage stem cells; ELSCs: epiblast-like stem cells; BLSCs: blastomere-like stem cells; nyd: not yet determined; Percentage within solid tissues: percentages of cells recovered following first cryopreservation step after isolation from solid tissues by mechanical disruption and enzymatic digestion; Location within solid tissues: based on cells isolated from tissues by mechanical disruption and enzymatic digestion; CD10, CD13, CD90, MHC-I: shared lineage CD markers for germ layer lineage (ectodermal, mesodermal, endodermal) stem cells; na: not applicable; Cryopreservation: DMSO: dimethyl sulfoxide; Freezing Proc: freezing process whereby frozen cryovials containing cells are either directly immersed in liquid nitrogen for flash freezing or placed in a low temperature freezer at designated temperature to allow a slow drop in temperature of approximately one degree per minute; Thawing Proc: thawing procedure whereby frozen cryovials containing cells are quickly brought to ambient temperature by either immersion in 37 °C water bath or rubbing hands together to allow body heat to thaw cells; % Recovery: the average percentage of cells recovered starting with the second time the cells are cryopreserved; dep: dependent; Susp cult: growth of cells in suspension culture; Response to proliferation agent(s): response to proliferation agent(s) such as platelet-derived growth factors; Activity in SFD medium w/o inhibitory agents: activity in serum-free defined medium in the absence of fibroblast feeder layer, recombinant-human leukemia inhibitory factor, recombinant-murine ESGRO, and/or recombinant-human anti-differentiation factor; LIF activity pre-confluent: response of cells to leukemia inhibitory factor prior to confluence being reached in cell cultures containing serum-free defined medium + inductive factors; LIF activity post-confluent: response of cells to leukemia inhibitory factor after confluence surpassed in cell cultures containing serum-free defined medium + inductive factors; Dependent variable to LIF: the limiting variable to the induction inhibitory activity of leukemia inhibitory factor on cells; Concentration of LIF: concentration of LIF necessary to prevent induction of lineage commitment in cells; ADF activity pre-confluent: response of cells to anti-differentiation factor prior to confluence being reached in cell cultures containing serum-free defined medium + inductive factors; ADF activity post-confluent: response of cells to anti-differentiation factor after confluence surpassed in cell cultures containing serum-free defined medium + inductive factors; Dependent variable to ADF: the limiting variable to the induction inhibitory activity of anti-differentiation factor on cells; Concentration of ADF: concentration of anti-differentiation factor necessary to prevent induction of lineage commitment in cells; Response to progression agent(s): such as insulin, insulin-like growth factor-I, or insulin-like growth factor-II that accelerate the phenotypic expression of differentiated tissue and/or lineage-committed precursor cell types; Response to inductive agent(s): such as general inductive agents (i.e., dexamethasone) and specific inductive agents (i.e., bone morphogenetic protein-4, basic-fibroblast growth factor, transforming growth factor-beta, skeletal muscle morphogenetic protein, etc.) that cause stem cells to commit to their respective downstream lineage-committed tissue and/or cell types.

* Work performed by others.

across all 3 primary germ layer lineages. It responds to brain-derived neurotrophic factor by forming cells belonging to the ectodermal lineage. It responds to bone morphogenetic protein-4 by forming cells belonging to the mesodermal lineage. And it responds to hepatocyte growth factor by forming cells belonging to the endodermal lineage. As long as the pluripotent stem cell remains lineage-uncommitted it is unresponsive to progression agents (i.e., insulin, insulin-like growth factor-I, insulin-like growth factor-II, etc.) that accelerate the time frame of expression for tissue-specific phenotypic differentiation expression markers. The pluripotent stem cell remains quiescent in a serum-free environment lacking proliferation agents,

lineage-induction agents, progression agents, and/or inhibitory factors, such as recombinant human leukemia inhibitory factor (LIF), recombinant murine leukemia inhibitory factor (ESGRO), or recombinant human anti-differentiation factor (ADF).^{4, 5, 7} Cells with characteristics similar to pluripotent stem cells have been isolated from brain, bone marrow, blood, dermis, inner ear, and skeletal muscle.^{4, 5, 8-15} Based on developmental nomenclature,² Young *et al.*⁴ designated their adult-derived pluripotent stem cell as an epiblast-like stem cell.

The 2nd category of precursor cells consist of 3 separate subsets of cells. Each cell displays a normal karyotype. Germ layer lineage ectodermal stem cells

will only form cells belonging to the ectodermal lineage. Germ layer lineage mesodermal stem cells will only form cells belonging to the mesodermal lineage. And germ layer lineage endodermal stem cells will only form cells belonging to the endodermal germ layer lineage. Germ layer lineage stem cells have both shared and unique patterns of cell surface markers. These stem cells demonstrate extensive capabilities for self-renewal, far exceeding the replicative clock for progenitor cells or differentiated cells. Germ layer lineage stem cells are telomerase positive. This characteristic is consistent with their extensive capabilities for self-renewal. They retain this capacity as long as they remain uncommitted to particular tissue and cell types within their respective lineages. However, once germ layer lineage stem cells commit to a particular tissue type they become tissue-specific progenitor cells. Like all progenitor cells they then exhibit a replicative clock of 8-10 population doublings for rodent cells¹⁶ or 50-70 population doublings for human cells¹⁷ before programmed cellular senescence and death occur (Table I) (Young HE, Hawkins KC, Boev A, Graves D, Holland BH, Stout CL *et al.* Compartmentalization of native pluripotent stem cells in the testis, brain, heart, and pancreas of adult rats. Submitted to Anat Rec; 2005. Young HE, Duplax C, Vourc'h P, Chesselet MF, Yost MJ, Ericson K *et al.* Adult-derived stem cells and their potential for tissue repair and molecular medicine. Submitted to J Cell Molec Med, 2005).^{1, 3-5, 18-21} Germ layer lineage stem cells are responsive to proliferation agents such as platelet-derived growth factors. They exhibit contact inhibition at confluence *in vitro*. These stem cells are unresponsive to lineage-induction agents that have actions outside their germ layer tissue lineage. For example, germ layer lineage mesodermal stem cells respond to bone morphogenetic protein-4 (which acts on cells of the mesodermal lineage), but do not respond to brain-derived neurotrophic factor (which acts on cells of the ectodermal lineage), or to hepatocyte growth factor (which acts on cells of the endodermal lineage). Germ layer lineage stem cells do not respond to agents that accelerate the time frame of expression for tissue-specific phenotypic differentiation expression markers. Germ layer lineage stem cells remain quiescent in a serum-free environment lacking proliferation agents, lineage-induction agents, progression agents, and inhibitory factors (Table I).^{1-4, 7}

²¹ Germ layer lineage ectodermal stem cells have been isolated from associated brain tissues, skeletal muscle,

dermis, fat, and skin (Vourc'h P, Lacar B, Mignon L, Lucas PA, Young HE, Chesselet MF. Neurturin induces proliferation and process outgrowth on cells with neurogenic potential isolated from the adult skeletal muscle. Submitted, 2005).^{2-5, 22-25} Germ layer lineage mesodermal stem cells have been isolated from adipose tissue, bone marrow, breast, dermis, granulation tissue, and skeletal muscle.^{2, 4, 5, 7, 18-20, 26-31} Germ layer lineage endodermal stem cells have been isolated from liver, pancreas, dermis, and skeletal muscle.^{2, 4, 5, 32, 33}

The 3rd category of precursor cells is composed of a multitude of multipotent, tripotent, bipotent, and unipotent progenitor cells. Progenitor cells have a finite life span that begins at birth. Progenitor cells have a replicative clock of 8-10 population doublings for rodents¹⁶ and 50-70 population doublings for humans¹⁷ before programmed replicative cell senescence and cell death occur. Progenitor cells are preprogrammed to commit to particular cell lineages. They are unidirectional in their ability to form differentiated cell types. There are 4 subcategories of tissue-specific progenitor cells: unipotent, bipotent, tripotent, and multipotent progenitor cells. Progenitor cells may be unipotent, having the ability to form only a single differentiated cell type. A precursor cell of endodermal origin residing in the thyroid gland designated the thyroid progenitor cell is an example of a unipotent progenitor cell. This cell will form thyroid follicular cells.³² A progenitor cell may be bipotent, having the ability to form 2 differentiated cell types. A precursor cell of intermediate mesodermal origin located within the ovary and designated the ovarian stromal cell is an example of a bipotent progenitor cell. This cell will form granulosa cells and theca cells.³² A progenitor cell may be tripotent, having the ability to form 3 differentiated cell types. A precursor cell of mesodermal origin, the chondro-osteo-adipoblast, is an example of a tripotent progenitor cell. This cell will form chondrocytes (cartilage), osteocytes (bone), and/or adipocytes (fat cells).³⁴ A progenitor cell may be multipotent, having the ability to form multiple cell types. A precursor cell of ectodermal origin residing in the adenohypophysis and designated the adenohypophyseal progenitor cell is an example of a multipotent progenitor cell. This cell will form gonadotrophs, somatotrophs, thyrotrophs, corticotrophs, and mammatrophs.³² Progenitor cells for particular cell lineages have unique profiles of cell surface cluster of

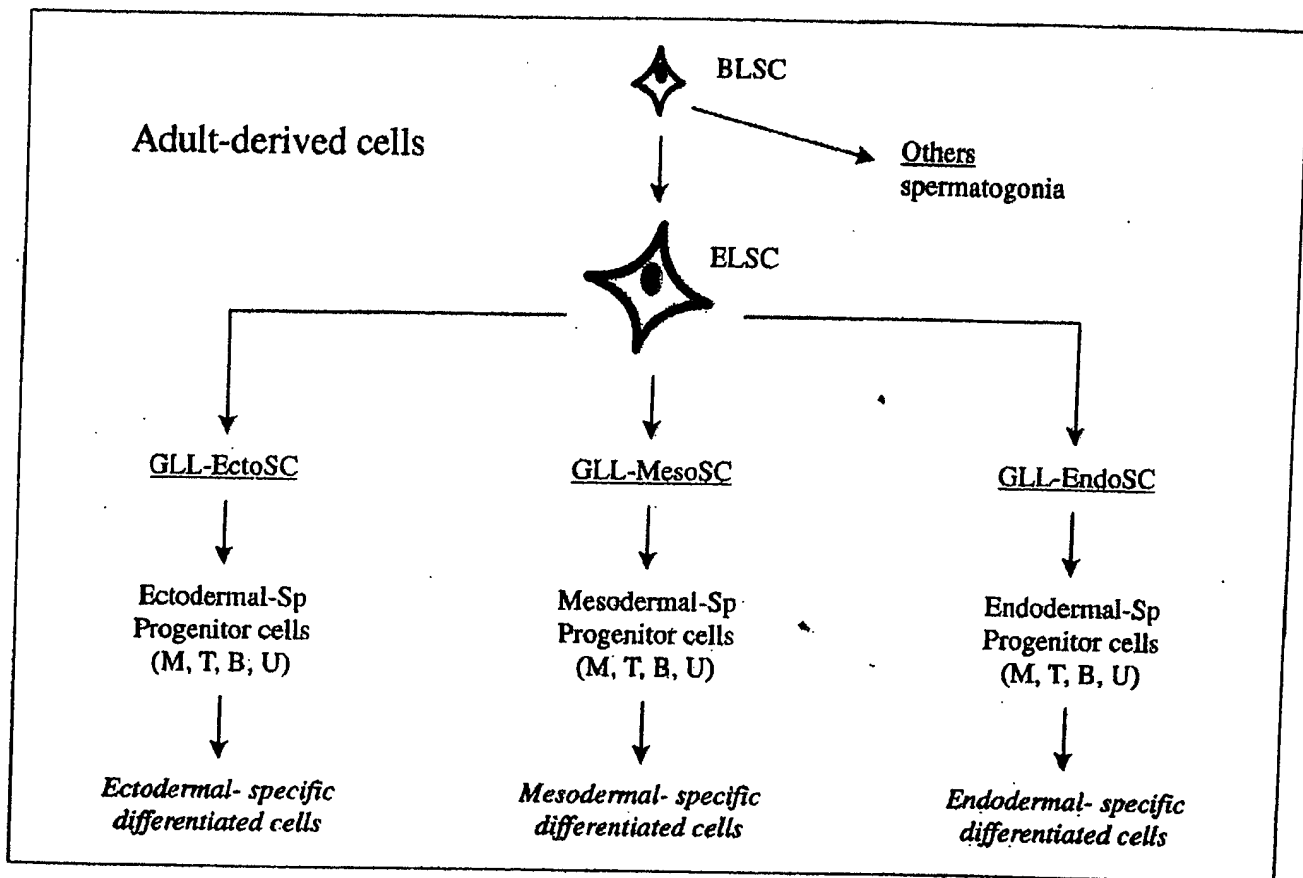


Figure 1.—Uni-directional differentiation pathway for adult-derived cells. BLSC: blastomere-like stem cell; ELSC: epiblast-like stem cell; GLL-EctoSC: germ layer lineage ectodermal stem cell; GLL-MesoSC: germ layer lineage mesodermal stem cell; GLL-EndoSC: germ layer lineage endodermal stem cell; Ectodermal-SP Progenitor Cells (M, T, B, U): ectodermal-specific progenitor cells (multipotent, tripotent, bipotent, and unipotent); Mesodermal-SP Progenitor Cells (M, T, B, U): mesodermal-specific progenitor cells (multipotent, tripotent, bipotent, and unipotent); Endodermal-SP Progenitor Cells (M, T, B, U): endodermal-specific progenitor cells (multipotent, tripotent, bipotent, and unipotent).

differentiation (CD) markers³⁵ and unique profiles of phenotypic differentiation expression markers.^{4, 5} Progenitor cells are responsive to proliferation agents such as platelet-derived growth factors. They exhibit contact inhibition at confluence *in vitro*. Progenitor cells are unresponsive to lineage-induction agents that have actions outside their tissue lineage. However, they are responsive to progression agents that accelerate the time frame of expression for tissue-specific phenotypic differentiation expression markers. Progenitor cells remain quiescent in a serum-free environment lacking lineage induction agents, progression agents, proliferation agents, and inhibitory factors (Table I). (Young HE, Duplaa C, Vourc'h P, Chesselet MF, Yost MJ, Ericson K *et al.*

Adult-derived stem cells and their potential for tissue repair and molecular medicine. Submitted to J Cell Molec Med, 2005).^{2, 4, 5, 7, 36} Multipotent, tripotent, bipotent, and unipotent progenitor cells have been isolated from a wide variety of tissues, including skeletal muscle, dermis, fat, cardiac muscle, granulation tissue, periosteum, perichondrium, brain, meninges, nerve sheaths, ligaments, tendons, blood vessels, bone marrow, trachea, lungs, esophagus, stomach, liver, intestines, spleen, pancreas, kidney, urinary bladder, testis, etc. (Young HE, Hawkins KC, Boev A, Graves D, Holland BH, Stout CL *et al.* Compartmentalization of native pluripotent stem cells in the testis, brain, heart, and pancreas of adult rats. Submitted to Anat Rec, 2005. Young HE, Duplaa C,

Vourc'h P, Chesselet MF, Yost MJ, Ericson K *et al.* Adult-derived stem cells and their potential for tissue repair and molecular medicine. Submitted to J Cell Molec Med 2005). 1, 2, 4, 5, 26, 32, 34, 37-54

We report here the discovery of a 4th category of adult-derived precursor cell. This precursor cell has thus far been isolated from skeletal muscle and testis of adult rat and from the skeletal muscle of the adult human. It has been partially characterized (Table I). This 4th category of adult-derived precursor cell, also composed of a single cell, has shown the potential thus far to form germ cells (spermatogonia) as well as all somatic cells of the body. This cell displays a normal karyotype. Based on developmental nomenclature,² we have designated this near-totipotent adult-derived precursor cell as a blastomere-like stem cell (Young HE, Duplaa C, Vourc'h P, Chesselet MF, Yost MJ, Ericson K *et al.* Adult-derived stem cells and their potential for tissue repair and molecular medicine. Submitted to J Cell Molec Med, 2005).

Uni-directional repair/differentiation model

The 5 categories of cells present in adult tissues, *i.e.*, differentiated cells, progenitor cells, germ layer lineage stem cells, epiblast-like stem cells, and blastomere-like stem cells, can be readily isolated and characterized based on multiple criteria, as shown in Table I. In a previous report, Young and Black² proposed a uni-directional model for adult stem cell differentiation. In their model the pluripotent epiblast-like stem cell was at the pinnacle of the hierarchy.² With the recent discovery of the near totipotent blastomere-like stem cells within adult tissues we would like to revise this model. In the revised version of this model (Figure 1) the blastomere-like stem cells are at the pinnacle of the hierarchy. They are the immediate precursor cells to the epiblast-like stem cells, which are the immediate precursor cells to the germ layer lineage (ectodermal, mesodermal, and endodermal) stem cells, which are the immediate precursor cells of the lineage-specific, (multipotent, tripotent, bipotent, and unipotent) progenitor cells, which are the immediate precursor cells to the differentiated cells. As discussed previously,² the precursor cells for each successive level have 4 options. The cells can either remain quiescent, they can proliferate, they can differentiate to the next level, or they can undergo apoptosis and die. In all our descriptive and experimental studies to date with

respect to stem cells, (Young HE, Hawkins KC, Boev A, Graves D, Holland BH, Stout CL *et al.* Compartmentalization of native pluripotent stem cells in the testis, brain, heart, and pancreas of adult rats. Submitted to Anat Rec, 2005. Young HE, Duplaa C, Vourc'h P, Chesselet MF, Yost MJ, Ericson K *et al.* Adult-derived stem cells and their potential for tissue repair and molecular medicine. Submitted to J Cell Molec Med, 2005. Vourc'h P, Lacar B, Mignon L, Lucas PA, Young HE, Chesselet MF. Neurturin induces proliferation and process outgrowth on cells with neurogenic potential isolated from the adult skeletal muscle. Submitted, 2005. 1-7, 18-22, 24, 36, 55-78 we have never seen either differentiated cells or precursor cells regress (*i.e.*, dedifferentiate) to a more primitive state. We have also not seen germ layer lineage stem cells of one lineage differentiate into cells of an entirely different germ layer lineage (*i.e.*, transdifferentiate). We therefore conclude that differentiation in adult precursor cells occurs only in one direction, from the most primitive cells to the most differentiated cell types. Future studies will address the specific locations of precursor cells within adult tissues and their involvement in tissue repair. The possible uses of these cells in tissue engineering and as delivery vehicles for molecular medicine will also be examined.

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Exhibit C

Phenotypic Bioassay as Assessed by Antibody Microarray ELICA

Our standard assay to assess the differentiation capabilities of any isolated cell line or cell clone utilizes a general induction medium coupled with an antibody microarray format (Young et al., 2004a,b, 2005). We utilize base medium (Opti-MEM), containing antibiotics, beta-mercaptoethanol, 10^{-8} M dexamethasone, 2 μ g/ml insulin, and pre-selected sera, i.e., SS9 and SS12, in our general induction medium. SS9 was selected for its ability to induce multiple mesodermal phenotypes. In contrast, SS12 contains inductive agents that induce the formation of both ectodermal lineage cells and endodermal lineage cells. The cell types that we currently have developed assays to detect include ectodermal lineage cells, mesodermal lineage cells, endodermal lineage cells, and "other" lineage cells (Table 1, below) (Young et al., 2004a).

In brief, 1000 cells are plated in each well of a 96-well plate in non-inductive plating medium. After 24 hours, the plating medium is removed and replaced with control medium (non-inductive plating medium) or the general induction medium (above). The cultures are fed every other day for 14-56 days. The cultures are stopped and assayed, utilizing the antibody microarray ELICA, to identify tissue specific phenotypic expression markers characteristic for specific cell types (Table 1).

Throughout my studies (1990-present) we have utilized this paradigm to identify particular populations of cells located in adult tissues. To date, we have recognized five categories of cells within adult tissues, i.e., differentiated cells (DC), progenitor cells (PC), germ layer lineage stem cells (GLSCs), pluripotent stem cells (PSCs), and totipotent stem cells (TSCs). The ELSCs/PPELSCs in this application are the pluripotent stem cells – in that they will form any germ layer lineage cell of origin (ectoderm, mesoderm, or endoderm), but in our hands have not formed spermatogonia.

Table 1

Induction of Phenotypic Expression in Native and Induced Adult Precursor Stem Cell

Lines as assessed by Antibody Microarray ELICA

Phenotypic	BLSC ⁰	ELSCs ¹	GLEctoSCs ²	GLMesoSCs ³	GLEndoSCs ⁴
Markers					
<u>Ectoderm</u>					
Neuronal	+	+	+	-	-
Progen Cells					
Neurons	+	+	+	-	-
Ganglia	+	+	+	-	-

Oligodendrocytes	+	+	+	-	-
Astrocytes	+	+	+	-	-
Radial Glial Cells	+	+	+	-	-
Keratinocytes	+	+	+	-	-

Mesoderm

Skeletal Muscle	+	+	-	+	-
Smooth Muscle	+	+	-	+	-
Cardiac Muscle	+	+	-	+	-
White Fat	+	+	-	+	-
Brown Fat	+	+	-	+	-
Hyaline Cartilage	+	+	-	+	-
Articular Cartilage	+	+	-	+	-
Elastic Cartilage	+	+	-	+	-
Growth Plate Cartilage	+	+	-	+	-
Fibrocartilage	+	+	-	+	-
Endochondral Bone	+	+	-	+	-

Intramembran.	+	+	-	+	-
Bone					
Tendon/	+	+	-	+	-
Ligament					
Dermis	+	+	-	+	-
Scar Tissue	+	+	-	+	-
Endothelial	+	+	-	+	-
Cells					
Hematopoietic	+	+	-	+	-
Cells					
<u>Endoderm</u>					
Endodermal	+	+	-	-	+
Progenitor					
Cells					
GI Epithelium	+	+	-	-	+
Liver Oval	+	+	-	-	+
Cells					
Liver	+	+	-	-	+
Hepatocytes					
Liver Biliary	+	+	-	-	+
Cells					
Liver	+	+	-	-	+
Canalicular					
Cells					
Pancreas	+	+	-	-	+
Progen Cells					
Pancreas	+	+	-	-	+

Ductal Cells

Pancreatic	+	+	-	-	+
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β -Cells

Pancreatic	+	+	-	-	+
------------	---	---	---	---	---

α -Cells

Pancreatic	+	+	-	-	+
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δ -Cells

Other

Spermatogoni	+	-	-	-	-
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a

Table Legend: ⁰BLSCs, blastomere-like stem cells (isolated and cloned); ¹ELSCs, epiblast-like stem cells (isolated and cloned); ²GLEctoSCs, germ layer lineage ectodermal stem cells (induced); ³GLMesoSCs, germ layer lineage mesodermal stem cells (isolated and cloned); ⁴GLEndoSCs, germ layer lineage endodermal stem cells (induced)

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Totipotent—Having unlimited capability. The totipotent cells of the very early embryo have the capacity to differentiate into extra embryonic membranes and tissues, the embryo, and all postembryonic tissues and organs.

Totipotent Stem Cells

Stem cells which are capable of forming every type of body cell. Each totipotent cell could replicate and differentiate and become a human being. All cells within the early embryo are totipotent up until the 16 cell stage or so.

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Many people are injured annually in the U.S. following so-called "medication errors".

[Learn about Medication Errors](#)**Google Refine Search with MedicineNet**☒ **Subscribe**[Learn more](#)**Definition of Totipotent****Totipotent:** Having unlimited capability.

A totipotent cell has the capacity to form an entire organism. Human development begins when a sperm fertilizes an egg and creates a single totipotent cell. In the first hours after fertilization, this cell divides into identical totipotent cells. Approximately four days after fertilization and after several cycles of cell division these totipotent cells begin to specialize.

Totipotent is as opposed to pluripotent and multipotent. Totipotent cells have totipotential. They specialize into pluripotent cells that can give rise to most, but not all, of the tissues necessary for fetal development. Pluripotent cells undergo further specialization into multipotent cells that are committed to give rise to cell that have a particular function. For example, multipotent blood stem cells give rise to the red cells, white cells and platelets in the blood.

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